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# The Effect Of Expectancy Of Analgesic Efficacy On Analgesic Effectiveness For Experimental And Clinical Pain

Manon Houle

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**THE EFFECT OF EXPECTANCY OF ANALGESIC EFFICACY  
ON ANALGESIC EFFECTIVENESS FOR  
EXPERIMENTAL AND CLINICAL PAIN**

**By  
MANON HOULE**

**Department of Psychology**

**Submitted in partial fulfilment of the  
requirement for a Doctoral Degree**

**Faculty of Graduate Studies  
The University of Western Ontario  
London, Ontario  
August, 1992**

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## ABSTRACT

The study evaluated the effects of expectation of analgesic efficacy on subsequent analgesic effectiveness for experimental and clinical pain. The experimental pain consisted of noxious heat pulses (45-51 °C) delivered to the inside of the forearm. After providing baseline visual analogue scale ratings (VAS) of the sensory intensity and the unpleasantness of the heat pulses, sixty subjects were divided into two groups—a hi-expectancy group, made to expect a potent analgesic and a lo-expectancy group, made to expect an ineffective drug. In either case, half of each group received a potent analgesic while the other half received a placebo. Forty-five minutes after receiving the analgesic or placebo, subjects rated the thermal stimuli again. The results showed significant analgesic main effect for expectancy but no main effect for drug. Thus, the experimental effect that is attributable mainly to psychological mechanisms was more powerful than effects attributable to pharmacologic action. In the second phase, the powerful effects of expectation of analgesic efficacy were evaluated in the context of post-surgical pain following extraction of impacted teeth. In this case, the sixty subjects were told that they would receive the same drug as they had received in the experimental pain context. Forty-five additional subjects acted as controls—a hi-expectancy control (n=15) group who believed they would receive a potent analgesic treatment, a lo-expectancy control (n=15) who believed they would receive an inert substance and an unaltered expectancy group (n=15) who received name brand Tylenol <sup>®</sup>3. In fact, all subjects received the pharmacological equivalent of Tylenol <sup>®</sup>3. After surgery, all subjects rated the sensory intensity and the unpleasantness of their post-surgical sensations over

the course of 3 doses of the drug. The results demonstrated the robustness of the effects of expectancy in the course of recovery from surgical pain. Convergent evidence also pointed to the importance of expectancies in a clinical pain context. High expectancies led to quicker return to work and reduced intake of narcotic and non-narcotic analgesics. The results are examined in light of the existing body of knowledge on pain perception and models of expectancy.

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## **CHAPTER ONE**

### **Review of the Literature**

Over the past 50 years, scientists who study analgesic effects have come to realize that a patient's expectation of the effectiveness of a given treatment can generate corresponding subjective post-treatment experiences. Research efforts have shown that one's expectation of the effectiveness of an analgesic treatment can be modified by factors such as: 1) direct past-experience with the analgesic (Batterman & Lower, 1968; Kantor, Sunshine, Laska, Meisner & Hopper, 1966; Laska & Sunshine, 1973; McGrath, Brooke & Varkey, 1981; Rickels, Lipman & Raab, 1966); 2) experimental enhancement or attenuation of expectancy (Batterman & Lower, 1968; Gregory and Diamond, 1973; McGrath et al., 1981; Voudouris, Peek & Coleman, 1985; 1989); 3) reducing stress and anxiety (Evans, 1974; 1985); 4) rendering the analgesic-giving ritual more or less "believable" (Buckalew, 1972; Wickramasekera, 1977) and 5) a subject's intrinsic or extrinsic personal motivation to respond to the drug (Totman, 1975). The purpose of the current investigation was to manipulate expectation for analgesic efficacy within an experimental pain context in an effort to isolate the independent effects of expectancy from the pure pharmacological effect of an analgesic. A subsidiary objective of the study was to assess how the expectations created in the experimental pain context influenced subjective experiences and evaluation of oral surgery. Still another objective was to examine the effects of expectancy on post-surgical pain and on the course of recovery from oral surgery. Finally, the study set out to examine the relationships among anxiety, imaginative involvement, expectations for pain and pain relief and subsequent reports of analgesic

effectiveness in an effort to shed light on how these measures interact with expectations to influence analgesia in both an experimental and a clinical pain setting.

2

The most important impetus for the recent emphasis on expectancy as an explanatory variable for responses to drug stems from the increased awareness of researchers and drug companies that response expectancies have an important impact on treatment outcome. In fact, it has become standard practice to employ a placebo condition as a baseline against which to assess the effects of active drugs. However, there have been surprisingly few studies which have systematically assessed the influence of response expectancies on analgesic efficacy. Most research endeavours in the area of analgesic efficacy have opted to "control" for expectancy effects using double-blind placebo designs rather than to isolate and quantify the effects of response expectancy using other specifically developed designs. The identification of the conditions (which patient under what conditions) under which expectancy effects could be minimized or maximized would allow clinicians to use expectancies as an adjunct to therapy rather than as an extraneous variable which needs to be controlled in drug studies.

Placebo studies have shown that approximately 35% of patients with severe clinical pain experienced pain reductions of at least 50% following the administration of a placebo (Evans, 1974). A review of the literature on non-specific factors (such as response expectancies) leads to the following conclusions: a) a subset of patients shows a significant therapeutic response to inert substances, objects or procedures; b) no procedure exists to identify this subset of patients in advance; c) a given patient does not respond to placebo in a reliable fashion; d) any object, inert substance or

procedure offered under the "right" conditions can generate a placebo effect; and e) the mechanism of the placebo effect is unknown and the "right" conditions are unclear (Wickramasekera, 1985).

Jensen & Karoly (1985) described three types of placebo effects: 1) symptom-centered placebo effects — the placebo produces an objective reduction in symptoms such as heart rate; 2) symptom-perception placebo effects — the placebo produces changes in subjects' perception of symptom such as changes in self-report of pain; 3) attributional placebo effects — the placebo acts on the reasons individuals give for symptom change such as the increased sexual arousal reported by subjects in response to placebo alcohol. According to Jensen & Karoly, the commonly quoted estimate that 35% of individuals respond to placebo treatment is based on only two types of placebo effects — symptom perception and symptom-centered effects. They argue that, if attributional placebo effects were measured and taken into account, a greater percentage of individuals would respond to placebos. In other words, if the effects of a placebo were measured not only against target variables (e.g. physiological measure of sexual arousal) but also against other variables such as subjective appraisal of sexual arousal (considered separately from the measure of physiological arousal), a greater proportion of subjects might be found to report placebo responses. For example, some subjects may report increased sexual arousal without any accompanying physiological evidence of sexual arousal. Jensen and Karoly argue that this change in attribution should also be considered a placebo response. In sum, little is known about the cognitive situational and contextual factors which mediate the relationship between expectation for pain relief and subsequent subjective experiences of analgesia.

Two recent lines of research used in the study of the effects of response expectancy provided a conceptual framework for the current investigation: 1) a burgeoning literature on the models which explain the development of expectancies and their manifestation (e.g. Kirsch, 1985; Marlatt & Rosehow, 1980; Siegel, 1983; Voudouris, Peck & Coleman, 1985; 1989); and 2) the use of balanced-placebo designs (in the placebo-alcohol literature) which can convincingly determine what portion of treatment effectiveness is due to the independent effects of expectation and what portion is due to the pharmacological effect (Marlatt & Rohsenow, 1980). A discussion of the literature which pertains to these two lines of research on response expectancies will be followed up by a review of the important methodological issues to consider in executing research on response expectancy and analgesic efficacy.

### Models

Recent years have seen the emergence of a number of research studies whose major purpose has been to develop models to explain placebo responding. Many of these models have dealt specifically with response expectancy to explain treatment effectiveness. Research endeavours in the areas of alcohol and alcoholism (e.g., Bridell, Rimm, Caddy, Krawitz, Sholis & Wunderlin, 1978; Lang, Goeckner, Adesso & Marlatt, 1975; Marlatt, Demming & Reid, 1973; Shapiro & Nathan, 1986), response to fear reduction treatment (e.g., Gatchel, Hatch, Maynard, Turns & Taunton-Blackwood, 1979; Paul, 1966) and response to hypnosis (e.g., Barber & Calverley, 1969; Council, Kirsch, Vickery and Carlson, 1983; Kirsch, Council & Vickery, 1984) have led to the development of models to help explain placebo effects and the role of response expectancy.

**The conditioned response model:**

In the 1950's and 1960's, theories of learning were most widely recognized as explanations for behaviour and behaviour change. The work of Herrnstein (1962) and Ross & Schnitzer (1963) has shown that placebo effects could be elicited in rats by means of classical conditioning procedures. In these studies insertion of a needle or injections of inert solutions produced responses like those obtained by a previously administered drug. From these studies and other studies conducted with humans (Knowles, 1963; Land and Rand, 1969) the conditioned response models evolved to explain the occurrence of placebo responding (Wickramasekera, 1980).

The conditioned response model uses an explicit classical conditioning model to explain the placebo effect. According to Wickramasekera (1980), the active treatment, in this case an analgesic, is the unconditioned stimulus (UCS), pain relief is the unconditioned response (UCR), and all the stimuli present during the administration of the analgesic (environmental, social and psychological stimuli) the conditioned stimulus (CS). After successful pairing of the CS-UCS resulting in pain relief (UCR), the CS alone can produce a conditioned analgesic response (CR). As within the classical conditioning paradigm, the placebo response (CR) is viewed as a learned fractional component of the UCR (Hull, 1952). The model predicts that a variety of inert substances, persons, procedures, events or places can come to function as CS's for the alleviation of pain provided they have been associated with the onset of a powerful UCS (or offset of the UCR) which relieves pain symptoms. Conversely, the pairings of CS-UCS which do not result in pain relief or which result in pain exacerbation produce the attenuation and the negation of subsequent similar CS-UCS pairings

(placebo hyperalgesia). Wickramasekera (1977) also suggested that vicarious experiences can, through association with active ingredients (UCS), establish neutral places, persons or procedures as CS's for the relief of discomfort or pain.

Empirical support for the conditioning model of the placebo occurrence comes primarily from animal studies (Herrnstein, 1962; Ross & Schnitzer, 1963). The author is aware of only two studies to date which have attempted to condition an analgesic placebo response in human subjects (Voudouris, Peck and Coleman, 1985; 1989). In their experimental pain studies, Voudouris et al. (1985; 1989) have surreptitiously paired placebo administration (topical cream) with an increase in the painful stimulus for half the subjects and with a decrease for the other half. Subjects' ratings of "constant levels of the experimental pain" were assessed both before and after this pairing. They found that subjects who experienced a conditioning history in which the placebo was effective (the intensity of the pain stimulus was decreased surreptitiously) reported significantly lower pain intensity in response to the "constant levels of the experimental pain" than did subjects who experienced a conditioning history in which the placebo was less than effective (the intensity of the pain stimulus was increased surreptitiously).

The authors conclude that their data provide support for Wickramasekera's conditioned response model since both placebo (analgesic) and nocebo (hyperalgesia) responses were conditioned. They also conclude that in this case, conditioning experience was more important than subjects' expectation for analgesia at producing changes in pain ratings.

McGrath, Brooke & Varkey (1981) showed that expectancy as determined by

past-experience with an analgesic was more important in predicting analgesic efficacy than the presence or absence of a pharmacologically active ingredient. In the study, subjects participated in two sessions — an experimental pain session using tooth pulp stimulation and a clinical pain session following extraction of impacted wisdom teeth. During the first session, half the subjects received a placebo while the other half received fentanyl (narcotic). In the second session, all subjects expected to receive the same drug. In fact, half the subjects who received a placebo in the first session (lo-expectancy) received a placebo while the other half received fentanyl. Similarly, half the subjects who received fentanyl in the first session (hi-expectancy) also received fentanyl in the second session whereas the other half received a placebo. The results showed that while producing significant pain reduction in hi-expectancy subjects, fentanyl did not reduce pain in lo-expectancy subjects. Similarly, placebo resulted in increases in subjective reports of pain in lo-expectancy subjects and slight reductions in pain for hi-expectancy subjects.

Kirsch (1985; 1991) argues that since different studies have demonstrated placebo effects that are either inconsistent or unrelated to the pharmacological effects of the drug being tested, classical conditioning should be viewed as one of the mechanisms by which expectancies are acquired (as demonstrated by McGrath, Brooke & Varkey, 1981) rather than as a mutually exclusive alternative to a cognitively-based expectancy theory. Using a balanced-placebo design, different studies in the alcohol literature have demonstrated placebo effects that are inconsistent with the pharmacological effects of alcohol but consistent with the culturally held beliefs about the drug. For example, although the pharmacological effect of alcohol is to decrease

sexual arousal (Rubin and Henson, 1976), the belief that one has consumed alcohol results in increased sexual arousal to erotic stimuli (Bridell et al., 1978; Wilson and Lawson, 1976). Similar results were obtained for aggressive behaviour (Lang, Goeckner, Adesso and Marlatt, 1975) and increased craving for consumption of alcohol (Marlatt, Demming and Reid, 1973).

Other studies have demonstrated placebo effects that are unrelated to the pharmacological effect of the drug being tested. For example, Knowles (1963) demonstrated decreased reaction times (placebo effect) to decaffeinated coffee (placebo) that are unrelated to the usual effects of caffeine. In this study, mean reaction times were shortest immediately following the ingestion of caffeine or placebo and increased at subsequent assessments (60 and 90 minutes). At the 60 minute assessment, reaction times for the caffeine, placebo and control conditions were virtually identical. At the 90-minute assessment, reaction times for the caffeine and placebo groups were significantly slower than under the control condition. Because effective blood levels of caffeine are not likely to be reached for at least 60 minutes following oral ingestion of caffeine (Goodman and Gilman, 1985), caffeine would need to produce shorter reaction times 60 mins. after ingestion of caffeine in order for caffeine to be considered an unconditioned stimulus for decreased reaction time. Slower reaction times at 60 minutes after ingestion of caffeine were not observed. Thus, the decreased time observed in the caffeine and placebo groups immediately after ingestion of the beverage could not have been due to conditioning.

Although it has been demonstrated that prior experience (conditioning trials) enhances the effects of placebo analgesia (Batterman & Lower, 1968; Evans, 1974;



Voudouris et al., 1985; 1989), other studies have shown that conditioning trials can inhibit the effects of placebo tranquilizers (Pihl and Altman, 1971; Rickels et al, 1966). One might attempt to explain this inhibition of the placebo effect as a compensatory conditioned response (Siegel, 1983; Siegel, Hinson and Krank, 1978; 1981; Siegel & McRae, 1984). According to this model, ingestion of morphine or a tranquilizer (UCS) would result in analgesia or sedation (UCR) as well as a compensatory conditioned response opposite to the drug effect (in this case hyperalgesia or arousal). Using this model, the CR for morphine would be hyperalgesia (Siegel, 1983), thus, it would follow that the analgesic response obtained following administration of placebo morphine (Evans, 1974) could not be due to conditioning (since the CR is hyperalgesia). However, there is considerable controversy about the compensatory conditioned response model because a number of studies which have failed to detect compensatory conditioned responses (e.g., MacRae and Siegel, 1987; Maude-Griffin and Tiffany, 1989).

In light of this evidence, it seems to be an oversimplification to characterize the placebo response as merely a CR that is a learned fractional component of the UCR. Instead, the placebo response should be viewed as a complex process that varies according to cognitive and contextual parameters such as anxiety, motivation or control.

### **Cognitive Theories:**

It is apparent that the explanatory power of the traditional learning theories could be increased by including cognitive mediating mechanisms. As early as 1932, Tolman presented animal data to support his interpretation that learning results in a

new cognitive organization which in turn mediates subsequent performance—reinforcement affected the speed at which a task was learned but not the degree of learning. Contemporary research has also shown that during modelling and observational learning, individuals can learn by observing others being reinforced (Bootzin, 1985; Rosenthal and Bandura, 1978).

Little research in the area of pain and analgesia has concentrated on testing models of expectancy for therapeutic outcome. The lack of research in this area can probably be attributed to the fact that, until recently, situational and contextual variables were seen as artifacts which needed to be controlled for in pain research.

Most of the research on cognitive models of expectancy was done in the area of fears and phobias. A classic research study on systematic desensitization (Paul, 1966) has shown that an expectancy modification procedure was more effective than a no-treatment control condition. A number of studies have demonstrated that a compelling expectancy modification procedure was as effective as a systematic desensitization condition (Kirsch & Henry, 1977; Kirsch, Tennen, Wickless, Saccone and Docy, 1983; McReynolds, Barnes, Brooks and Rehagen, 1973; Slutsky and Allen, 1978). Expectancy modification treatments have also been reported to be as effective as relaxation (when used as an active coping skill) (Gatchel, Hatch, Watson, Smith & Gass 1977) and heart-rate biofeedback (Russell and Lent, 1982). Several cognitive expectancy models have been proposed to explain the therapeutic impact of expectancies. The most significant models are reviewed.

**Cognitive Expectancy Model Derived from Classical Conditioning.** Reiss (1980) argues that Pavlovian conditioning is itself a cognitive process. Reiss

hypothesizes that an expectation about the occurrence (or non-occurrence) of an unconditioned stimulus (UCS) or a change in the magnitude or duration of a UCS is learned during Pavlovian conditioning. Conditioning is not the only way to change expectancies; cognitive learning and the observation of a model can produce a significant change in expectancies.

Although Reiss applies this model to phobias, it is also possible to apply the model to analgesic treatments. The model would predict that any treatment which could change a person's expectation about the occurrence, magnitude or duration of pain through associative learning over several trials would result in pain relief. Thus, according to this model, personal or vicarious past experience with analgesics would modulate expectancies for pain relief. The model also postulates that compelling expectancy manipulations (e.g., such as the believable treatment rationale given to the expectancy control group) can also produce pain relief. This model could explain why placebos sometimes produce effects which are unrelated to the pharmacological effects of the drug by invoking the role of cognitions and response expectancies.

Unfortunately, however, it fails to predict whether or under what circumstances conditioning will be more influential than expectancy manipulations in determining treatment outcome. Thus, it is impossible to know *a priori* whether past experience with an analgesic will be more likely than expectancy manipulations to modulate treatment outcome.

**The Selective Monitoring Models of Placebo Responding.** Skelton & Pennebaker (1982) postulated that individuals monitor their internal and external environments selectively for perceptions that fit their prior expectations. If

expectancies are for analgesic efficacy, individuals will selectively pay attention to internal and external cues which are congruent with analgesic effects. This selective response explains why people who expect an analgesic often report side-effects which are commonly associated with the ingestion of analgesics. Similarly, individuals may also report side-effects which are believed to be associated with the ingestion of a pharmacologically active agent. Another possibility is that individuals may focus on positive changes after receiving a placebo. They may emphasize small positive changes in their conditions and downplay the significance of negative changes (Lick and Bootzin, 1975). Individuals may also choose to interpret ambiguous somatic sensations according to their expectancies and thus label them as positive changes (Dinnerstein and Halm, 1970).

These explanations can parsimoniously explain subjective perceptions of symptoms that were prescribed in the drug or placebo giving ritual. However, they do not explain how objectively monitored physiological states are altered by placebos as in the case of an increase in endogenous opiate level following placebo analgesia (Levine, Gordon and Fields, 1978).

**Attribution Theory and the Role of Expectancies.** Ross & Olson (1981) explain placebo effects using the classical attribution theory (Schachter & Singer, 1962). They postulate that individuals use their reaction to the treatment (or the placebo treatment) to make inferences about themselves and their symptoms. If the perceived reaction to the treatment matches the expected reaction, then the model predicts that no changes in beliefs or expectancies are made. However, when a discrepancy exists between the obtained and the expected reactions to treatment, the

individuals will alter their beliefs about themselves or their symptoms to explain the discrepancy. Ross & Olson discuss this model mostly in terms of the attributions individuals make regarding their disease process — a process which they call inductive placebo effects. However, they do not extend the model to account for expectancy effects which produce subjective changes in symptom intensity (e.g., reduction in perceived pain intensity) or subjective changes in symptoms reporting (e.g., reporting side effects to a medication). Instead, they provide a review of studies which have attempted to explain expectancy effects and they proposed the following five properties of the placebo effect: 1) the direction of the placebo effect is related to the effect of the drug to which it is being compared — a placebo analgesic will produce analgesic effects whereas a placebo treatment aimed at systematic desensitization will reduce fear; 2) the strength of the placebo effect is proportional to the strength of the drug effect — a placebo used as a baseline against which to compare morphine is more potent than a placebo used as a baseline against which to compare aspirin (Evans, 1974); 3) the side effects of a placebo are often similar to the side effects of the drug to which they are compared<sup>1</sup>; 4) the short-term time-effect curve is similar for the placebo and the drug to which it is being compared; and 5) the drug and the placebo show similar dosage effects — two placebos are better than one (Rickels, Hesbacher, Weise, Gray and Feldman, 1970).

**Motivation as an explanation of non-specific analgesic effects.** Only a few studies have examined the effects of motivation on analgesic placebo responding.

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<sup>1</sup> This conclusion cannot be extended to alcohol studies which have shown placebo effects that are inconsistent with the pharmacological effects of alcohol but consistent with the culturally held beliefs about the effects of alcohol.

Totman (1975) provided 2 experimental groups with an analgesic injection. Members of one group were told that they would be paid for their participation, while those in the other group were told that they would not be paid. According to the cognitive dissonance theory, subjects who did not expect to be paid for their participation would have greater motivation to respond to placebo because a response would provide them with justification for subjecting themselves to a painful injection. The authors predicted that if motivation is related to placebo responding, the unpaid group would display greater analgesic effects than the paid group. As predicted, those subjects who were told that they would not be paid reported the greatest levels of analgesia.

Gibbons, Stefan & Hormuth (1981) in a series of three experiments have demonstrated that the way individuals respond to placebos is dependent in large part on the kind of effect he/she is expecting and the kind of effect he/she would like to experience. In the first experiment, they have shown that subjects found a performance-inhibiting drug more effective than a performance-facilitating drug because it provided them with an excuse for failure at a difficult problem-solving task. Interestingly, subjects who received the performance-inhibiting drug not only reported that the drug was more effective, but also attempted and solved a significantly greater number of problems while feeling that they had put less effort into the tasks. In the second and third experiment, the researchers attempted to determine whether placebo attributions reflect a motivational bias. In a 2 x 2 factorial design, they showed erotic or non-erotic movies to males who were high or low on a trait they called sex guilt. All subjects were given an arousal placebo. The authors hypothesized that high-guilt males would be threatened by the arousal produced by the erotic movie, and, consequently, would

attribute more of that arousal to the placebo than would low-guilt persons. The results supported the hypothesis and showed that high-guilt subjects reported more reaction to the placebo when it was available as a safe alternative to their reaction to the stimulus. Since this occurred only in the threatening stimulus condition, the authors concluded that the misattribution was motivated by a desire to maintain self-esteem. This study demonstrated quite convincingly that motivational factors have an influence not only on attributional placebo effects (i.e. reasons subjects gave for increased sexual arousal), but also on performance placebo effects (i.e. whether or not the placebo would produce changes in sexual arousal).

Jensen and Karoly, (1991) attempted to clarify the effects of motivation on symptom perception following ingestion of a placebo sedative. Half the subjects read instructions designed to increase their motivation to respond to the drug. Failure to respond was interpreted as being related to a negatively presented personality type whereas responding to the drug was interpreted as meaning that the person had a positive personality type. The other group of subjects was not presented with such motivations. Then, on 2 consecutive days, subjects were given a high dose and a low dose of placebo sedative. This study was done in a classroom setting with healthy undergraduates. Sedation level was assessed by asking subjects to describe their reaction to the drug by checking the adjectives which corresponded to their symptoms. Specifically, adjectives relating to stimulant effects received a score of 1, while adjectives relating to a depressant effect received scores of -1. The sum of these scores was used as an index of sedation. Manipulation checks indicated that the manipulations produced the desired alterations in motivation and expectancy.

However, the results consistently indicated that subjects who received instructions to increase their motivation to respond to a placebo sedative tended to endorse adjectives associated with sedation more than those subjects who did not receive the instructions. Unfortunately, the study was designed so that the independent effects of expectancy could not be segregated from the effects of motivation manipulation. The authors concluded that their study provided clear support for a motivational view of placebo responding. However, no evidence was provided to indicate that subjects were not simply responding according to the demand characteristics clearly established by the experimental instructions and procedure.

These studies show that in an experimental context, motivation to respond to a placebo seems to be important especially when it is manipulated so that the individual has a personal need to experience the symptom(s) in response to experimental demands or to reduce cognitive dissonance.

The experimental evidence suggests that there is a need to consider the motivational biases of the placebo recipients, so as to predict more accurately the kinds of effects which the placebos are likely to produce. However, it is difficult to examine the effects of motivational components without inadvertently affecting response expectancies and experimental demand characteristics. In analgesic studies, the effects of motivation could be assessed by testing the effects of an analgesic placebo in both lo-motivation and hi-motivation pain contexts. The lo-motivation pain context could be short-lasting, non-threatening experimental pain while the hi-motivation pain context could be severe pain following a difficult procedure such as surgery.

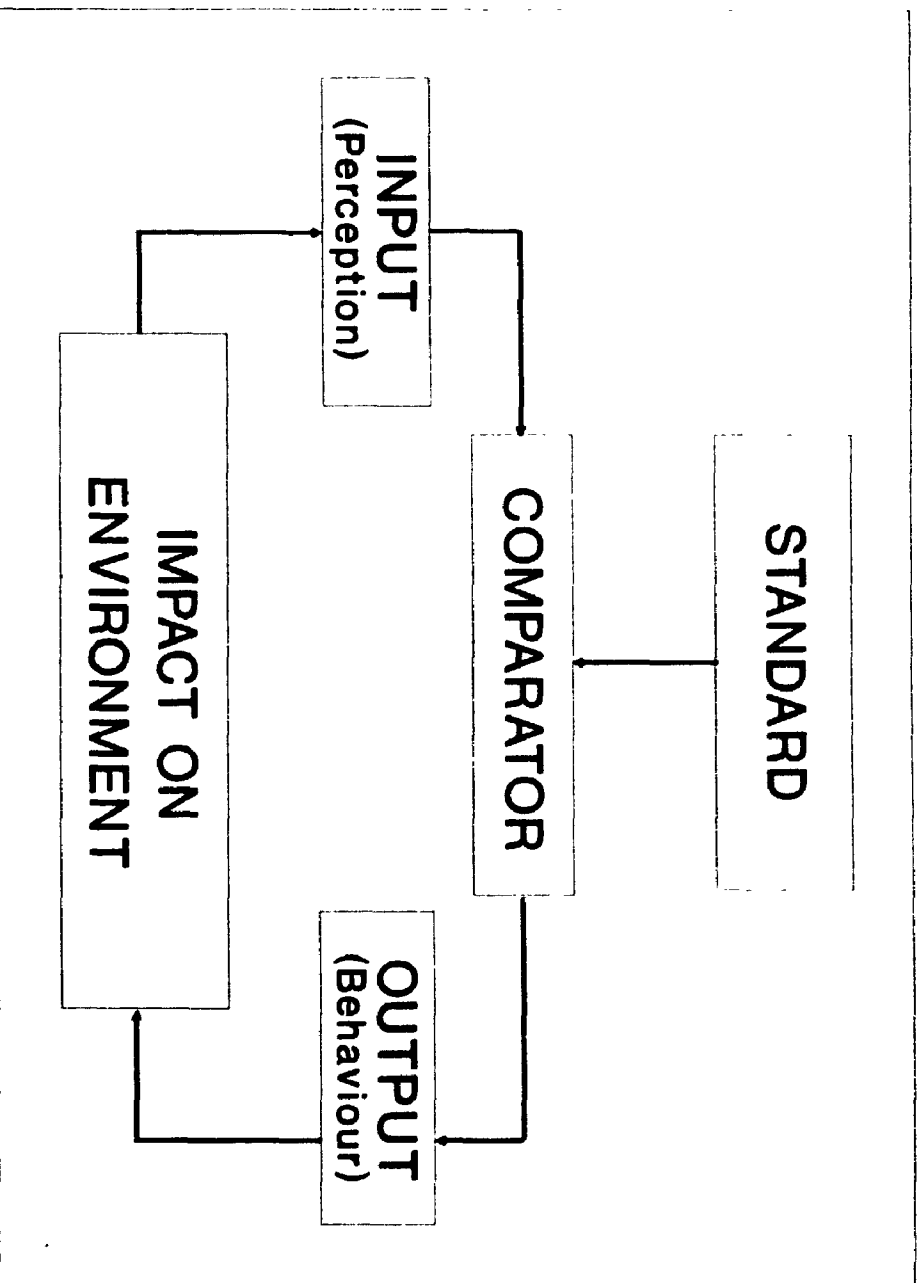
**Anxiety as a mediator of placebo responding.** It is a generally held belief



that placebo administration could produce a reduction in anxiety which may in turn produce a decrease in the level of pain perception. McGlashan, Evans and Orne (1969) examined the effect of two types of anxiety (state and trait) on subjects' pain threshold and pain tolerance to experimentally-induced ischemic muscle pain. They found that after the placebo (presented as a "strong pain killer") was ingested, situational anxiety increased. This increase in situational anxiety correlated only with an increased pain threshold, but not with pain tolerance (Evans, 1974). Interestingly, Evans (1974) characterizes this finding as a result which is contrary to previous impressionistic data. Trait anxiety was related to increases in pain tolerance. That is, the higher the level of trait anxiety subjects experienced, the larger the increase in pain tolerance after ingesting a placebo. Thus, the results suggest that the anxiety-relieving effects of analgesic placebo administration would be more important for subjects who experience a high level of generalized anxiety.

**The Control Theory and the Role of Expectancies.** Jensen & Karoly (1985) used control theory (Carver & Scheier, 1982) to explain placebo responding. According to this model, the building block of human behaviour is the negative feedback loop. Figure 1 illustrates the loop. In this model, perceptions (input functions) are compared against a reference value (standard). If a difference exists between the perception and the standard, the individual makes an attempt to alter the environment to reduce the discrepancy. The environment is examined again and alterations are made until there is no discrepancy between perception and the standard. According to the control theory, the goal of behaviour is to minimize the discrepancy between the perception and the standard.

Figure 1 The Negative Feedback Loop.



Jensen & Karoly postulate that placebo effects can be seen as an output whose goal is to minimize the perception of discrepancy. They propose that the standard is influenced by: 1) the individual's expectancies, and 2) the individual's motives. Thus, responses to treatment that are both expected and desirable in a particular context make up the standard for symptom perception.

After placebo treatment, a discrepancy is created and according to this model, the individual will produce an output to minimize the discrepancy. The researchers propose that the following four events can lead to a reduction in discrepancy:

- 1) The perception of the symptom(s) is altered to match the standard. Attention is not focused on analgesic cues.
- 2) The symptom is altered so that the subject's perception of it matches the standard.
- 3) Beliefs about the efficacy of the treatment are modified to force the standard to match the perception.
- 4) Beliefs about the underlying severity of what is causing the symptoms are altered so that symptoms are seen as being more or less resistant to change.

According to Jensen & Karoly, placebos can be seen as altering standards and placebo effects can be viewed as attempts to reduce the discrepancy caused by the introduction of the placebo.

According to this model, placebo effects will only occur when expectancy manipulations are believed or when individuals are motivated to respond. The extent of placebo responding should also be directly proportional to the level of expectancy and motivation to respond. This effect should be more significant in individuals who

have a greater propensity to focus on and be aware of internal events. Support was found for the hypothesis that increased self-focused attention is related to increased changes in the standard (Gibbons, Carver, Scheier & Hormuth, 1979; Scheier, Carver & Gibbons, 1979).

Although not explicitly stated by Jensen & Karoly, an increase in expectancies and/or motivation given as an adjunct to an active treatment could also produce changes in perception under the same mechanisms. However, the model does not allow for a prediction of the type of behaviour (output) that will result. For example, a patient who expects an analgesic but instead is given a placebo, will experience a discrepancy between the standard and the comparator. The model predicts that the individual will minimize the discrepancy with one of the four behaviours: 1) alter the report of pain perception to match the standard — will report analgesia; 2) alter perception of pain to match the standard — will perceive analgesia; 3) alter expectations about the drug to match the standard — will believe that the drug is ineffective; 4) believe that the physiological cause of the pain is worse than he/she had originally anticipated — the condition must be worse because the analgesic is not working. Although the model can successfully explain placebo effects of any kind, it unfortunately does not allow for *a priori* predictions of the individual's response. In fact, it could be argued that the model they propose is not falsifiable.

### **Designs to Study Effects of Expectancy**

As previously discussed, it is now recognized that the administration of drugs provides non-specific cues (such as expectancy) which can enhance the effects of the drug. Consequently, placebos are used as a baseline against which to assess the effects

of a drug.

In order to understand the development of designs that control for response expectancies, it is necessary to examine the historical development of designs aimed at controlling for placebo effect.

### **Study Designs**

Patient expectancy, experimental demand characteristics, experimenter bias and other situational variables have often been clumped together under the label of "nonspecific" factors (Rosenthal, 1966) which contribute to the placebo response in treatment evaluation studies. The double-blind placebo design has been used in an attempt to control for patients' expectations and experimenters' expectations by keeping both ignorant of the drug administered. Unfortunately, the extent to which double-blind methodology controls for subjects' expectations depends on the instructions given at the outset of the study (Marlatt & Rohsenow, 1980). While it is often ethically necessary that subjects be given information about medication prior to their involvement in the study, knowing that they may or may not receive an active drug might make subjects focus their attention away from analgesic effectiveness (Hurst and Weldner, Radlow and Ross, 1973). Instead, they might focus their attention inward and try to guess what treatment was administered. This experience might be quite different for subjects who have or who have not taken the drug before.

In fact, Margraf, Ehlers, Roth, Clark, Sheikh, Agras and Taylor, (1991) have demonstrated that in a randomized, double-blind comparison of three drugs, the great majority of patients and their physicians were able to rate accurately whether an active drug or a placebo had been given. An additional problem we face when interpreting

results of double-blind placebo design studies is that often, little information is given about what subjects are told at the outset of the experiment or about the subjects' past experience with the drug. Thus, the major difficulty of the double-blind placebo design is that it fails to provide a test for the "pure" effects of the analgesic alone or the placebo alone, unconfounded by subjects' expectations of receiving either a drug or a placebo. Marlatt and Rohsenow (1980) conclude that a between-group designs in which each group receives either a drug or a placebo is preferred in any research in which expectancy effects may influence the outcome.

Within the alcohol literature, research on expectancy effects has resulted in the development of the balanced placebo design. In this 2 x 2 factorial design, half the subjects are told that they will receive an active drug (in this case alcohol) whereas the other half are told that they will receive a non-active drug (in this case a non-alcoholic beverage). Within each group, half of the subjects receive an active drug and half do not. Thus, the following four conditions are included: a) expect a placebo/receive placebo; b) expect placebo/receive drug; c) expect drug/receive placebo; and d) expect drug/receive drug. Refer to Figure 2 for a description of the four cells of a balanced placebo design.

**Figure 2            Balanced Placebo Design**

		Subject Expects	
		Placebo	Drug
Subject Receives	Placebo	CELL A <i>'pure' control condition</i>	CELL B <i>'pure' expectancy effect</i>
	Drug	CELL C <i>'pure' pharmacological effect</i>	CELL D <i>expectation-augmented pharmacological effect</i>

The rows represent the drug administered and the columns represent the drug subjects expect to receive. Within this design, expectancy main effects are seen in the comparison of Cells B and D with Cells A and C. Main effects for the pharmacological effects of the drug are seen in the comparison of Cells A and B with Cells C and D. In this way, the balanced-placebo design can provide statistically orthogonal indices of the effects of the drug and the effects of expectancy (Marlatt & Rohsenow, 1980). Alcohol studies which used the balanced-placebo design have generally reported that expectancy had a greater effect on subjects' psychological and physiological responses than did the presence or absence of alcohol (e.g., Abrams & Wilson, 1979; Hull & Bond, 1986; Marlatt & Rohsenow, 1980; Polivy, Schueneman & Carlson, 1976; Vuchinich, Tucker & Sobell, 1979).

The successful implementation of the balanced-placebo design depends on several factors including: a) the persuasion of subjects that they are in fact receiving the drug they were told they would receive; and b) a stringent control for experimental demand characteristics (Collins & Searles, 1988; Knight, Barbaree & Boland, 1986; 1988; Weber & Cook, 1972). In alcohol research, the precautions taken to ensure the credulity of subjects include: 1) mixing the drinks in front of subjects; 2) administering a breathalyser test which provides false feedback; 3) rinsing with mouthwash to mask the detection of the presence or absence of alcohol; 4) masking the presence of alcohol by adding lemon juice to the drinks or mixing alcohol with a mixer which has an overpowering taste.

*Prima facie*, the use of the balanced-placebo design in analgesic research would not seem to require as many decoys to ensure subject credulity because the presence or

absence of an analgesic can be easily dissimulated in a gelatin capsule. In analgesic research, the problem arises however in ensuring that the gelatin capsules administered to subjects create markedly different sets of expectations. It is also important to make sure that low expectancy instructions are vague enough to allow subjects, who unknowingly receive the drug (Cell C) to report pain reductions without feeling that they responded in a manner which was contrary to their perceived experimental predictions.

The successful implementation of the balanced-placebo design therefore also calls for stringent control of experimental demand characteristics. Extant studies in alcohol research have shown that methodological precautions such as ensuring that the experimenter is blind to group assignment and that subjects' expectancies are assessed at the end of the study (subjects guess their group assignment and how much alcohol they consumed) are necessary conditions to ensure an accurate interpretation of the results obtained in a balanced-placebo design (Collins & Searles, 1988; Marlatt & Rohsenow, 1980). Another precaution which would further decrease experimental demand characteristics would be to keep subjects ignorant of the existence of other treatment conditions. Because of the deception involved, ethical limitations often restrict the use of such methods in clinical research.

In sum, the balanced-placebo design seems to be the method of choice to segregate the effects of expectancy from the pharmacological effect of a drug. Extant research with the balanced-placebo design in alcohol research points to the need to give special attention to methodological issues when implementing this design in a study of the effects of expectancy on analgesic effectiveness.



### **Methodological Considerations**

Recent advances in pain research have led to the emergence of a number of studies which use laboratory analogue pain stimulation to elucidate the psychological and physiological mechanisms of pain perception. Concurrently, there has been a move to: 1) perfect the laboratory pain stimuli so that the results obtained would be generalizable to clinical pain; and 2) perfect the methods of pain measurement so that meaningful statements could be made about the quality and the extent of change in pain perception after treatment. The following sections present the work from which state-of-the-art methods of laboratory pain induction and pain measurement have evolved.

#### **Laboratory Analogue Pain Stimulus**

According to Price (1988), to be used as a laboratory analogue, a pain induction procedure must meet several criteria in order to achieve maximum validity. One prerequisite for external validity is that the painful stimulus activate those receptors and nerves which are predominantly associated with nociception (A $\delta$  and C). To achieve internal validity, the analogue pain stimulus should allow for multiple presentations of discrete (ie., not outlasting the period of stimulation) and quantifiable stimuli over a short period of time so as to minimize errors in measurement and reduce the incidence of subjects responding in a manner which conforms to the perception of experimental demand characteristics. It has been demonstrated that the extent of analgesia reported by subjects after receiving a cognitive therapy for pain in a laboratory setting depends on the type of painful stimulus used to assess analgesic effectiveness (Houle, McGrath, Moran & Garrett, 1988). The study showed that in the same subjects, tooth pulp stimulation, which allows for randomly delivered discrete pain sensations, lent itself to

different pain reductions under experimental conditions than did cold pressor stimulation which consists of sensations that progressively increase from cold to severe pain and outlast the period of stimulation.

The thermal stimulator is a proven method for inducing valid and reliable pain stimuli in the laboratory. With the thermal stimulator, pulses can be delivered at various intensities throughout the range from threshold (45°C) to tolerance (51°C). A small thermistor placed at the tip of the probe permits direct measurement of the temperature at the thermode/skin interface allowing for controlled and quantitatively measured production of heat stimuli. The active cooling device within the probe allows for discrete presentation of noxious stimuli after which the skin temperature is immediately returned to baseline. The thermode is held by the experimenter to allow maximum consistency across stimuli and across subjects. Because extensive research has been done with this device (e.g., Miron, Duncan & Bushnell, 1989; Price, Barrell & Gracely, 1980; Price & Harkins, 1987; Price, Harkins, Rafii & Price, 1986; Price, Rafii, Watkins & Buckingham, 1984; Price, Von der Gruen, Miller, Rafii & Price, 1985; Price, Harkins & Baker, 1987) there is the added advantage of permitting the comparison of results across studies.

### **Pain Measurement**

**Multidimensional character of the pain experience.** Until recently, pain has been treated as though it were a sensory quality which varies only in intensity (Melzack, 1983). Developments in pain research and pain measurement have led to a multidimensional view of painful stimuli. Some of the dimensions which have been investigated are: a) sensory-discriminative - which refers to the location, quality,

duration and intensity of the sensation; b) arousal - which describes the extent to which pain dominates one's experience and interferes with ongoing thoughts and intentions; and c) affective - which refers to the unpleasantness of the sensation (Price, 1988).

Since painful experiences have unique qualities beyond their differences in sensory-intensity, a complete understanding of a clinical or experimental pain experience cannot be achieved without an accurate assessment of the various dimensions which make up the painful experience. Further, a multi-dimensional assessment of a painful experience can shed some light on the mechanism by which a particular pain treatment works. For example, different types of analog pain studies have shown that cognitive factors (such as a reduction in anxiety) can selectively reduce the affective dimension of the painful experience. Gracely, McGrath and Dubner (1978) have shown that 5 mg of diazepam (a tranquillizer) significantly reduced the subjective ratings of unpleasantness to painful electrocutaneous shock without altering subjective ratings of sensory-intensity. In another study, Gracely, McGrath and Dubner (1979) demonstrated that subjective ratings of the sensory-intensity and the affective dimensions of tooth pulp stimulation could be selectively reduced by fentanyl (a narcotic) and saline placebo, respectively. It has also been demonstrated that decreasing one's expectation of avoiding pain by warning subjects before they received noxious heat pulses resulted in a decrease in the magnitude of unpleasantness responses but did not affect subjective ratings of sensory-intensity (Price, Barrell and Gracely, 1980). Clearly, the assessment of pain dimensions other than the traditional "painfulness" has allowed these investigators to give a better description of the process by which the pain treatments under investigation affect the

manner in which subjects rate pain.

Since the outcome of studies which examine treatment efficacy and pain mechanisms may depend on the dimension of pain assessed (Gracely, Dubner and McGrath, 1982; Gracely, McGrath & Dubner, 1978, 1979; Price, Barrell and Gracely, 1980) the use of a single dimension of the painful experience is not warranted. In fact, Gracely and Dubner (1987) have shown that the conclusions that can be reached concerning the effect of a particular treatment for pain may depend on the dimensions of the pain examined. They showed that in certain instances, the experience of side-effects only, without accompanying analgesic effects can produce reports of reductions in the painfulness of stimuli. In their study, verbal judgements of the global "painfulness" showed a pattern of results inconsistent with either the subjective ratings of sensory-intensity or unpleasantness. Subjective ratings of sensory-intensity were reduced significantly after administration of fentanyl but not after saline placebo. Addition of a pre-injection of diazepam to increase the experience of side-effects did not alter these findings. Conversely, subjective ratings of unpleasantness were reduced after saline placebo but not after fentanyl. A pre-injection of diazepam did not alter these effects. Verbal judgements which focused only on the "painfulness" of the sensations showed that fentanyl alone or in combination with a pre-injection of diazepam produced significant analgesia similar to that obtained with sensory-intensity ratings. However, the combination of diazepam and saline placebo produced results different from those produced by saline placebo alone. With a pre-injection of diazepam, saline placebo resulted in significant reductions in the verbal description of painfulness. Since diazepam has no analgesic effect, this result can only be attributed

to the experience of side-effects by subjects. Gracely and Dubner (1987) concluded that the verbal description of painfulness does not represent a simple combination of all the dimensions of the painful experience and shows that responses to an inert placebo, an active placebo and an analgesic can vary with the type of pain assessment procedure used.

**Magnitude estimation methods of pain measurement.** Psychophysical methods of pain measurement have evolved from traditional methods such as pain and tolerance thresholds to contemporary methods such as ratio scales and magnitude estimation methods (Bonica, Liebeskind & Albe-Fessard, 1979; Price, McGrath, Rafii & Buckingham, 1983). Traditional methods of measurement yield indirect measures of pain expressed in units of stimulus intensity while contemporary methods yield direct measures of pain expressed in subjective units of sensation magnitude (Lodge, 1981; Stevens, 1975).

In a review of the principal criteria for an ideal pain assessment procedure, Price (1988) has proposed that the pain measurement method should: 1) have ratio scale properties; 2) be free of biases inherent in different psychophysical methods; 3) separately assess the intensity and the unpleasantness dimensions of pain; 4) provide information about the accuracy and reliability of the subjects' performance of the scaling responses; 5) be useful for both clinical and experimental pain and allow for reliable comparison between both types of pain; 6) be reliable and generalizable; 7) be sensitive to changes in pain intensity; 8) be simple to use. There is no consensus as to which of the pain measures best fulfils these criteria. However, pain measures which yield ratio scales, as opposed to interval scales are preferable because they allow for

meaningful interpretation of the magnitude of the sensation (Lodge, 1981; Stevens, 1975) while also allowing for comparisons between different types of pain (Gracely and Dubner, 1981; Price et al., 1983; Price, 1988).

Recently, psychophysical methods of magnitude estimation have been used so that ratio scales of pain measurement could be derived (Price, Barrell & Gracely, 1980; Price & Harkins, 1987; Price et al., 1984; Price et al., 1986; Price et al., 1983). The use of ratio scales allows for meaningful statements about pain intensities, such as "my pain was reduced by 50%". Visual analogue scales (VAS) which are 150 mm lines used to rate the magnitude of sensations, have been validated as ratio scales of measurement for both chronic, and experimentally-induced heat pain (Price et al., 1983). In Price et al, 1983, subjects used VAS to rate the strength and the unpleasantness of heat stimulation and adjusted thermal pain intensity to match the lowest, usual and highest intensities of chronic pain. The power functions derived for the intensity and affect of pain produced by noxious heat pulses predicted the strength and the unpleasantness of pain for different levels of stimulus intensity and for different levels of chronic pain. The power function exponents ( $y=kx^a$ ) for noxious heat stimuli in different studies yielded consistent results. The exponents for pain intensity are between 2.1 and 2.2 and those for pain unpleasantness are between 2.4 to 2.7 (Price et al., 1980; Price et al., 1983; Price et al., 1986).

Price (1988) has reviewed the possible factors which could lead to biases in the use of visual analogue scales to measure pain. He notes that to reduce bias, it is necessary to instruct subjects carefully about the use of VAS and to present them with the entire range of stimulus intensities beforehand. To be most sensitive to changes in

sensory intensity and least vulnerable to biases in rating, visual analogue scales which aim to measure pain should be between 10 to 15 cm in length and clearly delineate extremes such as "the worst pain imaginable" (Seymour, Simpson, Charlton and Phillips, 1985; Stevens and Marks, 1980).

The use of magnitude estimation procedures in pain measurement gives the added advantage of allowing for comparisons across studies. In the past 15 years, magnitude estimation methods for pain measurement have been used to assess the effectiveness of various treatments on clinical and experimentally induced pain. The treatments investigated were: exogenous opiates such as morphine (Price, Vonder Gruen, Miller, Rafii and Price, 1985), fentanyl (Gracely & Dubner, 1987; Gracely, McGrath and Dubner, 1979; Price, Harkins, Rafii and Price, 1986);  
b) electroacupuncture (Price, Rafii, Watkins and Buckingham, 1984); diazepam (Gracely & Dubner, 1987; Gracely, McGrath and Dubner, 1976); hypnotic analgesia (Houle, McGrath, Moran and Garrett, 1988; Price and Barber, 1987); and placebo (Gracely and Dubner, 1987). A review of the outcome of these studies has led Price (1988) to propose two generalizations which could shed light on the mechanisms by which these varied treatments affect pain perception.

The first generalization is that exogenous opiates or treatments believed to activate central opiate mechanisms (eg. acupuncture) produce significant reductions in both the sensory-intensity and the affective components of the pain experience. Price also points out that the pattern of change in pain perception following opiate analgesia is quite characteristic. A given dose of opiate reduces different intensities of pain sensations by a nearly constant numerical extent and not by a constant percentage —

that is low intensity pains are reduced to a greater extent than sharp intense pains. In addition, opiates have equal effects on the sensory and affective components of experimental pain but reduce the affective component of clinical pain by a greater degree than the sensory-intensity component (Price et al., 1986). The second generalization is that in an experimental pain setting, methods which aim at reducing anxiety result in significant reductions in the affective rather than the sensory-intensity dimension of pain perception. The reductions in the affective component are more pronounced for lower intensity stimuli than for higher intensity stimuli. The treatments which results in such reductions are diazepam, placebo and hypnosis (Price, 1988).

Thus, laboratory analogue studies should use a pain induction procedure which allows for multiple presentations of discrete and quantifiable stimuli over a short period of time in order to minimize errors in measurement and reduce the incidence of subjects responding in a manner which conforms to their perception of experimental demand characteristics. The contact thermode is one of the pain stimuli which best fits these criteria. Studies which aim to shed light on psychological or physiological processes of pain perception should view pain as a multidimensional experience and measure pain with valid and reliable ratio scales (such as VAS) which permit meaningful interpretations of the changes in pain perception which occur after treatment. An additional advantage to the use of ratio scales is that they permit comparisons with other studies.

In summary, attempts to quantify the independent contribution of expectancy of analgesic efficacy on subsequent responses to an analgesic have been limited in scope. Although several models have been proposed to explain the development of



expectancies and how they manifest themselves to influence treatment outcome, there is no model to date which can predict who will respond to expectancies and under what conditions. In the context of analgesics, it has long been recognized that expectancies of treatment efficacy can enhance the effects of a drug. For this reason, placebo controls are typically used as a baseline against which to assess the effects of a drug. This chapter reviewed the problems with placebo controls and presented the balanced placebo design which allows for the assessment of the independent effects of a drug and of expectancy. Extant studies in the alcohol literature have demonstrated that expectancies can have extremely powerful effects — sometimes even stronger than the effects of alcohol. The balanced placebo design has never been used to parcel out the independent effects of expectancy from the effects of an analgesic. The review raised important methodological issues which must be considered in applying this model to the study of response expectancy and analgesic efficacy.

## **CHAPTER TWO**

### **Hypotheses**

#### **Overview**

On the basis of this review, a balanced placebo design was used in an experimental pain context to separate the independent pharmacological effects of Tylenol<sup>®</sup>3 from the expectancy of analgesic efficacy effects. Subsequently, the effects of expectancy of analgesic efficacy created in the experimental context were assessed over the course of recovery from oral surgery by telling subjects they would receive the same drug as they received in the experimental session but in reality surreptitiously administering the equivalent of Tylenol<sup>®</sup>3 to all participants.

In the experimental session, subjects provided subjective ratings of the sensory intensity and the unpleasantness of painful thermal stimuli applied to the inside of their forearms both before and 45 minutes after ingestion of a pill or pills. Subjects were separated into hi- and lo-expectancy levels. Hi-expectancy subjects were instructed that they would receive an analgesic plus an analgesic enhancer designed to help the body absorb the pain medication more effectively. In fact, half of the hi-expectancy subjects received a placebo while the other half received the same pharmacologically active ingredients as those found in Tylenol<sup>®</sup>3. Lo-expectancy subjects were informed that they would receive an analgesic enhancer only. In fact, half received a placebo while the other half received the pharmacological equivalent of Tylenol<sup>®</sup>3. Expectancy manipulation checks were used throughout.

The influence of expectancy of analgesic efficacy was also assessed in the surgical context. Specifically, the relations of expectancy and anxiety about surgery

and post surgical pain to recovery were examined.

For post-surgical pain, the subjects who participated in the experimental session were told that they would receive the same drug as they had received in the experimental session thus, creating a hi-expectancy and a lo-expectancy group. In fact, however, all subjects were given the pharmacological analgesic equivalent of Tylenol<sup>®</sup>3. An additional three groups of subjects who did not participate in the experimental phase were added as controls. The hi-expectancy control subjects were told they would receive an analgesic plus an analgesic enhancer to help the body absorb the pain medication more effectively. The lo-expectancy control subjects were told they would receive an enhancer only, without an analgesic. The third control group was an unaltered expectancy group whose subjects were told that they would receive and who in fact did receive Tylenol<sup>®</sup>3.

Based on the results of extant studies in the alcohol literature, it was hypothesized that in the experimental pain context, expectancy of analgesic efficacy would be a more important determinant of analgesic response than the presence or the absence of a pharmacologically active analgesic. Expectancy of analgesic efficacy was also expected to moderate analgesic effectiveness in the course of recovery from oral surgery. It was expected that subjects with a hi-expectancy of analgesic efficacy would experience significantly more post-surgical pain relief than subjects with a lo-expectancy of analgesic efficacy.

On the basis of the literature review, a series of hypotheses are proposed for each phase of the study (experimental, surgical and post-surgical). Specific questions derived from the literature review are imbedded within the hypotheses and will be

addressed separately in the Results Section.

### **Specific Hypotheses**

#### **Experimental Session**

##### **Hypothesis 1**

- a) It was predicted that expectancy instructions would produce greater expectation of analgesic efficacy in the hi-expectancy groups than in the lo-expectancy groups; these differences between the hi- and lo-expectancy groups were expected to be maintained after first-hand experience with the effectiveness of the medication in the experimental pain situation.
- b) Because they expected a more potent drug; it was predicted that after receiving the pills, hi-expectancy subjects would experience significantly less anxiety than lo-expectancy subjects.
- c) It was expected that the four experimental groups of subjects would experience different levels of anxiety reduction after having experienced the effects of the medication. Hi-expectancy/analgesic subjects were expected to experience the greatest reduction in anxiety followed by equal levels of reduction for the hi-expectancy/placebo subjects and the lo-expectancy/analgesic subjects. Lo-expectancy/placebo subjects were expected to have an increase in anxiety because they were to receive a lo-expectancy ineffective drug after surgery.
- d) It was expected that the number of side-effects reported would vary across groups. Specifically, hi-expectancy subjects were expected to report a significantly greater number of side-effects than lo-expectancy subjects because they expected a more potent drug.

## Hypothesis 2

It was predicted that expectations would have a greater effect on subjective reports of intensity and unpleasantness than the presence or absence of an analgesic.

Question i: As was suggested by Price (1988), will central inhibitory analgesia (produced by codeine) produce a characteristic pattern of analgesia marked by 1) equal reductions in both the sensory intensity and the unpleasantness component experimental pain; and 2) reductions of different intensities of pain sensations by a nearly constant numerical extent — that is responses to low intensity stimuli will be reduced to a greater extent than responses to higher intensity stimuli.

Question ii: As was suggested by Gracely, McGrath & Dubner (1979), will subjects in the hi-expectancy/placebo group experience a reduction in the unpleasantness rather than the sensory component of the noxious experience?

Question iii: Is placebo's effect primarily through a reduction in anxiety?

## Surgical Session

### Hypothesis 3

- a) Of the subjects who participate in the experimental session, those who experience the greatest levels of pain and unpleasantness relief are expected to:
  - 1) be less anxious and apprehensive about surgery; 2) rate the surgery as having been less difficult; 3) anticipate less post-surgical pain and unpleasantness.
- b) Subjects who participate in the experimental session are not likely to experience the full potency of the analgesic — even if they actually receive the analgesic, because an analgesic is not as potent in an experimental pain context as it is in a clinical pain context. Subjects who participated in the experimental session will be expecting to receive the same drug after surgery

as they received in the experimental session. Thus, when compared to control subjects, it is expected that experimental subjects will experience greater pre-surgical anxiety and apprehension about surgery and recovery from surgery.

### **Post-Surgical Session**

#### **Hypothesis 4**

It is predicted that expectation of analgesic efficacy will influence the level of analgesia experienced after surgery.

Specifically:

- a) It is expected that the three control groups (lo- and hi-expectancy, Tylenol<sup>®</sup>3) will differ in their levels of expectation for pain relief and subsequent reported analgesic experience. Because the lo-expectancy controls are expected to have the lowest level of expectation for pain relief, they are expected to experience the lowest level of post-surgical analgesia and unpleasantness reduction. In contrast, the hi-expectancy controls are expected to have the greatest level of expectation for pain relief as well as the greatest level of post-surgical analgesia and unpleasantness relief;
- b) It is predicted that expectancy levels also will be related to post-surgical analgesic efficacy and unpleasantness relief for the experimental groups. The hi-expectancy groups will report greater post-surgical pain and unpleasantness relief than the lo-expectancy groups. No difference is expected between the reports of analgesic efficacy and unpleasantness reduction of subjects who received an active analgesic and the reports

of those who received a placebo in the experimental session.

## **CHAPTER THREE**

### **Pilot Study**

Using a balanced-placebo design to parcel out the independent effects of expectation of analgesia from the "pure" pharmacological effects of the analgesic required that the instructions given to subjects during the experimental session produce the desired levels of expectancy for pain relief. Thus, the expectation for pain relief produced by both sets of instructions was assessed in a pilot study. The main purpose of the pilot study was twofold: 1) to ensure that high expectancy instructions were formulated so that they would produce higher expectation for pain relief than low expectancy instructions; 2, to ensure that low expectancy instructions were vague enough to allow subjects, who unknowingly received an analgesic, to report pain reductions without feeling that they were responding in a manner which was contrary to their perception of experimental predictions.

Eighty-six university students who attended an introductory psychology course at the University of Western Ontario rated the instructions. All subjects were given a booklet and were told that the purpose of the study was to "evaluate the instructions that we will give to participants in a study which investigates the effects of psychological factors on pain perception". Then, subjects were told to read the letter of explanation used in the study (APPENDIX J) and to imagine that they were taking part in the experiment described in the letter of explanation. Half the subjects read the low expectancy instructions first while the other half read the high expectancy instructions first.

The low expectancy instructions read as follows:



Today, I will give you a white capsule. The white capsule is made of sodium, calcium and plant extract. We know it is harmless, but we do not know its exact side-effects. We know that when it is taken with pain medication, it enhances the effects of the pain medication by helping the body absorb the pain medication more effectively. Today, we want to see what the effects of the capsule are alone. After you take the capsule, I will continue to monitor your blood pressure. After forty-five minutes, I will also ask you to rate the intensity and the unpleasantness of heat stimuli.

The high expectancy instructions read as follows:

Today, I will give you a white capsule along with a red and white pain capsule. The white capsule you will receive today is made of sodium, calcium and plant extract. We know it is harmless, but we do not know its exact side-effects. We know that when it is taken with pain medication, it enhances the effects of the pain medication by helping the body absorb the pain medication more effectively. After you take both capsules, I will continue to monitor your blood pressure. After forty-five minutes, I will ask you to rate the intensity and the unpleasantness of heat stimuli.

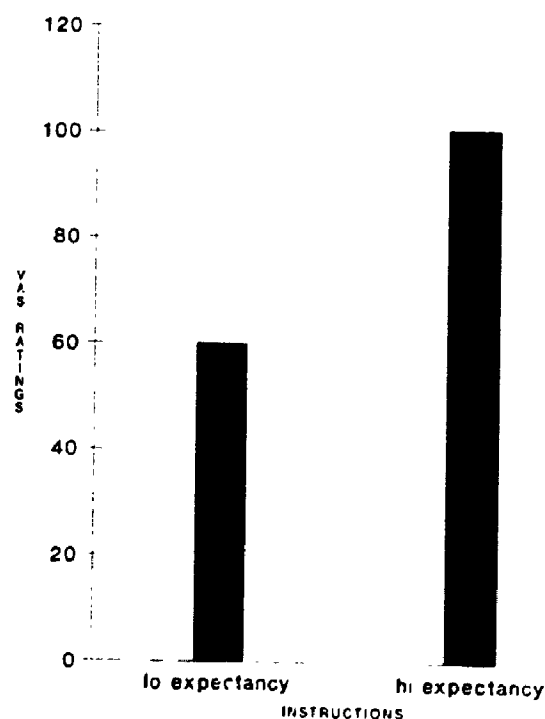
After reading the first set of instructions, subjects were asked to rate on a 150 mm visual analogue scale how they thought the capsule(s) would affect their pain sensitivity during the next hour. Then, subjects were asked whether they believed they would feel side-effects to the medication, whether they would feel comfortable in reporting side-effects if they experienced them and whether they would feel comfortable in reporting a decrease in sensitivity to experimental pain. After answering these questions, subjects were asked to forget about the instructions they had just read and read another set of instructions. Thus, the subjects who had been asked to read low expectancy instructions first were now asked to read high expectancy instructions. Similarly, subjects who had been asked to read high expectancy instructions first were now asked to read the low expectancy instructions.

After reading the second set of instructions, subjects answered the same questions as they were asked to answer after the first set.

As shown in Figure 3 subjects' ratings of expectation for pain relief for high and low expectancy instructions (collapsed across order because there were no significant effects for order  $F=.31$ ) revealed that high expectancy instructions produced significantly greater expectation for pain relief than low expectancy instructions ( $t = 4.76$ ;  $p < .01$ ).

An analysis of subjects' responses showed that although four subjects may have been doubtful that the white capsules could produce side-effects, all answered that they would nonetheless feel comfortable in reporting side-effects if they experienced them. After reading low expectancy instructions, all subjects responded that they would feel comfortable reporting pain relief if they experienced it. Thus, it was concluded that low expectancy instructions should not inhibit subjects who unknowingly receive an analgesic to report pain relief.

FIGURE 3. RATINGS OF EXPECTATIONS  
PRODUCED BY TWO SETS OF INSTRUCTIONS



## **CHAPTER FOUR**

### **Method**

#### **Subjects**

The subjects for this study were 105 adult patients (male = 50; female = 55) scheduled for extraction of one or more impacted teeth in the oral surgery department of the Faculty of Dentistry at The University of Western Ontario. The patients were between 18 and 47 years of age ( $M = 24.2$ ;  $s.d. = 4.9$ ). As compensation for their participation in the study, surgical fees were waived.

The criteria for inclusion in the study were as follows: a) extraction of one or more teeth requiring bone removal and soft tissue damage; b) no history of sensitivity or allergy to acetaminophen, codeine or milk; c) no history of abuse of codeine or other opiates. In addition, in cases where subjects used medication on a regular basis, the investigator ensured that there would be no cross-reactions with the components of the analgesic used in the study. These inclusion criteria served to: 1) protect subjects who could have experienced adverse effects from their participation; and 2) eliminate from the data pool the subjects who had extensive past experience with pain and/or analgesic drugs — since this could have influenced their expectations for pain relief in the proposed experiment.

Three patients declined to participate in the study. Of the patients who volunteered for the study, eight were eliminated. Two subjects were eliminated because they were unable to complete the questionnaires, two because they were suffering from chronic pain, one because he was allergic to some component of the analgesic, one because he was taking medication which would have had a cross-

reaction with acetaminophen and compromised his health, one because she was overly anxious to participate in the experimental phase of the study, and one because he did not return his completed questionnaire.

The majority of patients had only one impacted tooth (requiring bone removal) extracted at one time ( $n = 94$ ). Eleven patients had two impacted teeth (requiring bone removal) extracted at one time. Of the impacted teeth, 100 were third molars; two were second molars; five were first molars; six were other teeth (1-22; 1-23; 1-24; 1-14; 1-35; 1-45)

Sixty subjects participated in two sessions. During the first session (EXPERIMENTAL SESSION), subjects filled out a series of questionnaires and gave subjective ratings of the intensity and the unpleasantness of a series of noxious heat pulses delivered to the ventral portion of their forearm before and after receiving an oral dose of an analgesic or a placebo. During the second session (SURGERY SESSION) the effectiveness of the analgesic was assessed by having subjects rate the intensity and the unpleasantness of their post-surgical pain for a 9 to 12-hour period while receiving an oral analgesic. Forty-five more subjects acted as controls who participated in the SURGERY SESSION only and completed the series of questionnaires prior to surgery.

### **Questionnaires**

**Past Experience Questionnaire.** Information regarding age, past history of painful experiences, past experience with analgesics, past experience with dentists and expectations of pain during and after surgery was obtained for each subject (APPENDIX A). Subjects rated on 150mm VASs the strength and the

unpleasantness of their two most painful past experiences. The intensity and unpleasantness VASs were anchored as "not intense at all", "most intense pain imaginable", "not unpleasant at all" and "most unpleasant imaginable", respectively. The measurement (in mm.) from the left anchor to the subjective ratings were used in the analyses. Subjects' perception of the average levels of analgesia they had obtained from analgesics in general was also measured on a 150mm VAS. The VAS was anchored to the left and to the right by "does not get rid of any pain" and "gets rid of all the pain", respectively. The measurement from the left anchor to the subjective rating was used in the analyses. (This same value was used for all VAS within study).

An index of past experience with analgesic treatment was derived by dividing the subjects' approximation of the number of times they received an analgesic treatment by their chronological age. Perceptions of specific analgesic treatment efficacy was obtained by having subjects rate which two familiar analgesics are most effective and which two are least effective.

Information concerning general anxiety about dentists and specific anxiety about extraction of wisdom teeth was also collected. Verbal responses to these questions were coded as follows: "good, well, no problem" were given a rating of 1; "difficult, I am scared, I don't like it" were given a rating of 2; and "very difficult, I am terrified" were given a rating of 3. These numerical ratings were used in the analyses.

The purpose of the questionnaire was threefold: first, to determine whether subjects met the criteria for inclusion in the study; second, to permit analysis of the

relationship between subjects' past experiences with pain, drugs and analgesics and their developed expectations concerning pain and analgesia; and finally, to assess the presence and magnitude of specific anxieties which are unique to the dental setting.

**Expectancy Questionnaire.** The questionnaire was designed to evaluate subject expectancy of the effects of the pill(s) on their pain, blood pressure, heart rate and anxiety level (APPENDIX B). Subjects completed two versions of the questionnaires—immediately after and 45 minutes after ingesting the pill(s). Subjects used 150mm VASs to rate their expectancy of the pill(s) effects on their pain, blood pressure, heart rate and anxiety (immediately after taking the pill(s)) and their perception of the pill(s)' effectiveness (45 minutes after ingesting the pill(s)). The VASs were anchored on the extreme left and right by statements which indicated no effects and statements which indicated maximal effects, respectively. Subjects also used VASs to rate their anxiety levels immediately after and 45 minutes after taking the pill(s). The anxiety VAS was anchored to the left by "as relaxed as could be" and to the right by "the most nervous possible". The measurements (in mm.) from the left anchor to the subjective ratings were used in the analyses.

The two versions of the questionnaire presented the questions in a different order to reduce the chances of automatic responding.

**Spielberger State-Trait Anxiety Inventory** (Spielberger, Gorsuch, Lushene, Vagg & Jacobs, 1977). It was hypothesized that the cognitive events which accompany the pain and the stress of an experimental pain procedure and a dental pain procedure might vary as a function of anxiety. Accordingly, all subjects completed both forms of the State-Trait Anxiety Inventory (APPENDIX C). Each

form consists of 20 items to which subjects selected one of four answers (not at all, somewhat, moderately so, very much so). The raw scores which can range from 20 to 80 were used in the analyses.

**Tellegen's Absorption Scale** (Tellegen, 1976). This questionnaire is designed to assess whether subjects who score high on imaginative involvement would be better placebo responders. Absorption is the factor which predicts hypnotic suggestibility most reliably (Hilgard, 1979; Spanos & McPeake, 1975; Tellegen & Atkinson, 1974).

Accordingly, all subjects completed the 37-item Tellegen Absorption Scale to measure their ability for imaginative involvement (APPENDIX D). Subjects answered true or false to 37 statements describing ability for absorption in every day activities. The number of "true" responses was computed and makes up the raw score which ranged from 0 to 37. The raw scores were used for analysis.

**Side-Effects Checklist**. All subjects completed a side-effects checklist twice (20 minutes and 45 minutes after taking an analgesic or a placebo) to determine whether they experienced psychological and/or physiological side-effects to the medication (APPENDIX E). The side-effects included are those commonly associated with opiate analgesics. The analyses used the number of side effects endorsed by each subject.

**Pre-Surgery Questionnaire**. Immediately before surgery, each subject (except those in the Tylenol #3 group) rated their level of anxiety, anticipated pain unpleasantness during and after surgery (APPENDIX F) on 150mm VASs. All VASs were anchored at both extremities to the left, by positive statements (e.g. as relaxed as could be) and to the right by negative statements (e.g. most nervous possible).

The measurements (in mm.) from the left anchor to the subjective ratings were used in the analyses.

**Post-Surgery Questionnaire.** Immediately after surgery, each subject used 150mm VASs to rate their subjective evaluation of the surgery, the sensations experienced during surgery and expectations for pain relief after surgery. (APPENDIX G). The measurements (in mm.) from the left anchor to the subjective ratings were used in the analyses. Subjects also rated on a 4-point scale, how well surgery went compared to expected.

**Post-surgery home questionnaire.** Subjects completed a home questionnaire (APPENDIX H) designed to measure their experience of pain and unpleasantness for 3 doses of medication. Subjects used 150mm VAS to rate the pain and the unpleasantness of post-surgical sensations five times after the administration of each dose: a) immediately after; b) 1/2 hour after; c) 1 hour after; d) 2 hours after; e) 3 hours after. The intensity and the unpleasantness VASs were anchored to the left by "no sensation at all", "most intense sensation imaginable", "not unpleasant at all" and "most unpleasant sensation imaginable", respectively. The measurement (in mm.) from the left anchor to the subjective ratings were used in the analyses. Subjects also completed the McGill Pain questionnaire which yields measures of sensory, affective, evaluative and miscellaneous qualities of the pain experience. The sum of these scores also was used as a total pain rating.

Recovery measures included: number of hours until (1) eating, (2) eating normally and (3) returning to work. Subjects also provided ratings of how much pain they actually experienced compared to how much they had expected on a 150mm



VAS. The VAS was anchored to the left by "I experienced much less pain than I expected" and to the right by "I experienced much more pain than I expected". The measurement (in mm.) from the left anchor to the subjective rating was used in the analyses.

Subjects also rated their subjective perception of analgesic effectiveness on a 6-point scale ranging from "got rid of no pain" to "got rid of all the pain". The numerical value of the rating was used for analysis.

This questionnaire was designed to evaluate the relationship between expectancy, the experience of post-surgical pain and the speed of recovery.

**Surgeon Questionnaire.** This questionnaire was completed by the attending oral surgeon for each patient. The surgeons (1) described the extraction(s) performed and the extent of bone removed, (2) rated on 150mm visual analogue scales the difficulty of the procedure and their expectations of how much post-surgical pain the patients would experience (APPENDIX I). The VAS used to rate the difficulty of the procedure was anchored at the left and right extremities by "as easy as could be given the placement of the tooth" and "as difficult as could be given the placement of the tooth", respectively. The VAS used to rate the surgeon's prediction of the patients' level of post surgical pain also was anchored at both extremities: to the left by "no pain at all" and to the right by "excruciating pain". The measurement (in mm.) from the left anchor to the subjective ratings were used in the analyses.

### **Pain Induction Equipment**

The pain induction instrument used in this study was a thermal stimulator which generated thermal heat ranging from 41°C to 51°C through a hand-held contact

thermode. The contact thermode portion of the device was constructed and purchased from the Biomedical Instrumentation Facility, Medical College of Virginia. The contact thermode consists of a cylindrical piece of copper, 1 cm in diameter. The copper is covered with a thin layer of thermo-conductive epoxy in which a spiral nichrome wire (heater) is embedded. Water at 5-6°C is circulated through the copper cylinder. At the tip of the contact thermode is a thermistor which senses the epoxy surface temperature and through a feedback circuit controls the heater voltage to maintain or change the surface temperature. The power unit which generates current to drive the contact thermode was designed and constructed in the Department of Psychology workshop at the University of Western Ontario. The thermode is also equipped with an active cooling system which returns skin temperature back to 34°C immediately after delivery of a 1 sec heat stimulus. The cooling system consists of a cooler (27 cm x 40 cm x 35 cm) filled with 4 litres of water maintained between 5°C-6°C (Fisher brand thermometer #14-995-SB). A submersible utility pump (#23H1) from the Little Giant Pump Co., Oklahoma City, Oklahoma circulated the water from the cooler to the contact thermode.

### **Pain Measures**

Subjects used visual analogue scales (VAS), 150 mm long to rate both the intensity (VAS-I) and the unpleasantness (VAS-U) of noxious thermal sensations produced by the contact thermode. The endpoints of VAS-I and VAS-U were designated as the sensation is "not strong at all" and "as strong as could be" and "not unpleasant at all" and "the most unpleasant possible", respectively.

In order to standardize the scaling instructions and to clarify the distinction

between the intensity and unpleasantness dimensions of pain, all subjects were given the following instructions at the outset of their involvement in the study (these instructions are similar to those used by Price, McGrath, Rafii and Buckingham, 1983):

There are two aspects of pain which we are interested in measuring: the intensity, how strong the pain feels, and the unpleasantness, how unpleasant the pain is for you. The distinction between these two aspects of pain might be made clearer if you think of listening to a sound such as a radio. As the volume of the sound increases, I can ask you how loud it sounds and how unpleasant it is to hear it. The intensity of pain is like loudness; the unpleasantness of pain depends not only on intensity but also on other factors which may affect you. There are scales for measuring each of these two aspects of pain. Although some pain sensations may be equally intense and unpleasant, we would like you to judge the two aspects independently. Please mark the line to indicate the relative intensity of your pain sensation; the further to the right, the greater the intensity. Similarly, mark the other line to indicate the relative unpleasantness of the sensation.

### **Analgesic and Placebo Preparation**

Four types of capsules were prepared by the investigator for the various conditions of the study. The #1 gelatin capsules were filled (by the investigator) individually with the following ingredients:

<u>red and white placebo capsule</u>	- 300 mg of Carnation brand powdered milk,
<u>red and white analgesic capsule</u>	- 300 mg of powdered acetaminophen and 30 mg of codeine phosphate <sup>2</sup> ;
<u>white placebo capsule</u>	- 300 mg of Carnation brand powdered milk;
<u>white analgesic capsule</u>	- 300 mg of powdered acetaminophen and 30 mg of codeine phosphate.

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<sup>2</sup> The analgesic used in this study contains the same active ingredients in the same quantity as Tylenol<sup>3</sup>-- the analgesic most commonly used after extraction of impacted third molars.

After preparation, each capsule was weighed on a Mettler P1200 scientific scale distributed by Fisher Scientific. Each analgesic capsule weighed  $500 \pm 20$  mg.

### **Pharmacology of Tylenol <sup>®</sup>3**

A composition of acetaminophen and codeine combines the analgesic effects of a centrally acting analgesic, codeine, with a peripherally acting analgesic, acetaminophen. Both ingredients are well absorbed orally (McNeilab Inc., 1983). Codeine has been found to retain at least one-half of its analgesic activity when administered orally. Following absorption, codeine is metabolized by the liver and metabolic products are excreted in the urine (McNeilab Inc., 1983). Acetaminophen is distributed throughout most tissues of the body. Acetaminophen is metabolized by the liver. Although Tylenol <sup>®</sup>3 contains 15 mg of caffeine in addition to analgesic ingredients, it is unlikely that this substance influences the analgesic effectiveness of the analgesic ingredients. In fact, a study comparing the relative bioavailability of acetaminophen and codeine elixir showed that no significant difference existed between the two dosage forms (i.e. tablet vs. elixir) with respect to peak plasma concentration of peak time (McNeil Pharmaceutical, 1983). Therefore, the tablet formulation (which also contains 15 mg of caffeine) was bioequivalent to the elixir (which also contains 7% of alcohol).

### **PROCEDURE (Experimental Session)**

All experimental sessions were conducted in the same dental operation room in the Oral Surgery Division of the Faculty of Dentistry at the University of Western Ontario. Sixty subjects participated individually in a two-hour experimental pain session one or two days before undergoing surgical extraction of one or more impacted

impacted teeth. Subjects were recruited by M.H. who also conducted all sessions. After reading the letter of explanation<sup>1</sup> and signing the consent form (APPENDIX J), each subject completed a past-experience questionnaire (APPENDIX A). Once it was established that a subject met the inclusion criteria for participation in the study, each subject was trained to use visual analogue scales (VAS) to rate noxious thermal stimuli. Once the novelty of the stimuli was reduced, baseline ratings were obtained by having each subject use VAS to rate the intensity and the unpleasantness of at least four series of randomly presented noxious thermal stimuli to the inside of the forearm. In each series, stimuli of 45°C, 47°C, 49°C and 51°C were presented four times each in random order. The arm on which stimuli were applied and the order in which subjects rated the intensity and the unpleasantness dimensions of the sensation was counter-balanced across subjects and across sessions.

Subjects were randomly assigned to one of four cells of the balanced placebo design (see Figure 4A).

Of the sixty experimental subjects, thirty subjects received LO-EXPECTANCY instructions designed to make them believe that they would receive a drug with no known analgesic properties (cells A & C)<sup>4</sup>. Of the thirty subjects who received lo-expectancy instructions, fifteen took a white placebo (CELL A) and the other fifteen took a white analgesic (CELL C).

The remaining thirty subjects received HI-EXPECTANCY instructions

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<sup>1</sup> The standing committee on Human Research of the University of Western Ontario approved that subjects did not have to be told explicitly at the outset of the study that they would receive either a placebo or an active drug. This procedure reduced the experimental demand characteristics associated with this study.

<sup>4</sup> Refer to the PILOT STUDY for a transcript of the LO- and HI-EXPECTANCY instructions and a description of the test done to ensure that the instructions produced the desired levels of expectations for pain relief.

## FIGURE 4 STUDY DESIGN

## A - EXPERIMENTAL SESSION

n = 60

## SUBJECTS EXPECT TO RECEIVE

SUBJECTS RECEIVE	DRUG WITH UNSPECIFIC EFFECT	CELL A <i>white placebo</i>	CELL B <i>white placebo and red &amp; white placebo</i>
	ANALGESIC	CELL C <i>white analgesic</i>	CELL D <i>white placebo and red &amp; white analgesic</i>
		n = 30	n = 30

## B - POST-SURGERY SESSION

n = 105

	SUBJECTS WHO PARTICIPATED IN THE EXPERIMENTAL SESSION		SUBJECTS WHO DID NOT PARTICIPATE IN THE EXPERIMENTAL SESSION		
	n = 60		n = 45		
	lo	hi	lo	neutral	hi
	(subjects expect the same drug as they received during the experimental session)		(expect pill is analgesic enhancer)	(no instructions to alter expectations)	(expect analgesic & enhancer)
	white analgesic capsule	white placebo and red & white analgesic	white analgesic capsule	Tylenol 3	white placebo and red & white analgesic
Subject Actually Receives	n = 30	n = 30	n = 15	n = 15	n = 15

designed to make them believe that they would receive a potent analgesic (cells B & D).<sup>4</sup> Of the thirty subjects who received high expectancy instructions, fifteen took a combination of white placebo/red & white placebo (CELL B) and the other fifteen took a combination of white placebo/red & white analgesic(CELL D).

The experimenter was aware of the appearance of the capsules taken by the subjects, however, she was blind to the content of the capsules. The registered nurse in oral surgery dispensed the previously coded capsule containers to the experimenter thus ensuring a double-blind procedure.

In order to monitor the expectations produced by the instructions, all subjects rated their anxiety level and were asked to rate on VAS how they believed the capsule(s) would affect their blood pressure, pain sensitivity, heart rate and anxiety (APPENDIX B). Blood pressure was monitored three times after the subject ingested the capsule(s): immediately after; 20 minutes after; and 45 minutes after. A registered nurse was available in the clinic at all times to respond to any medical emergencies. Contact with University Hospital Emergency was also available.

During the 45-minute period allowed for the capsules to take maximal effect<sup>5</sup>, subjects were asked to complete a Tellegen Absorption Questionnaire (APPENDIX D), a side-effects Checklist (at 20 minutes and 45 minutes after taking the capsules) (APPENDIX E) and a State-Trait Anxiety Questionnaire (APPENDIX C). Forty-five minutes after taking the capsule(s), each subject used VAS to rate the intensity and the unpleasantness of the series of noxious stimuli (45°C-51°C).

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<sup>5</sup> Plasma acetaminophen concentration is maximal between 40 and 60 minutes while plasma codeine concentration is maximal between 40 and 90 minutes following oral administration (McNeil Pharmaceutical, 1983)

At the end of the session, subjects rated (on VAS) the effects of the capsules on their blood pressure, heart rate, anxiety and pain sensitivity (APPENDIX B). Before leaving, subjects were reminded not to drive nor operate heavy machinery for a 2 1/2 hour period after taking the medication. Subjects were also provided with a list of phone numbers and individuals to contact in case they experienced adverse effects from the medication.

### **Procedure (Surgery Session)**

All surgical procedures were conducted under local anaesthetic only at the oral surgery clinic of the Dentistry School of the University of Western Ontario.

In order to assess how the expectancy manipulations during the experimental session affected analgesic efficacy in a clinical pain situation, pre- and post-surgery data were obtained for fifty-seven of the sixty subjects who participated in the experimental session. One subject was too anxious to undergo surgery and the other two subjects underwent surgery which did not require bone removal.

Before surgery, all subjects had to sign a consent form which stipulated clearly that it was anticipated that bone removal would be required during surgery. In addition, the consent form stated all possible risks involved with the procedure. All subjects received this information prior to surgery.

Before surgery, the fifty-seven subjects completed a State Anxiety Inventory (Spielberger et al., 1987) (APPENDIX C) and rated on 150 mm VAS their anxiety, expectation for pain and unpleasantness during the procedure and their expectation for pain after surgery (APPENDIX F).

Then each subject was given 12 doses of the analgesic (300 mg of



acetaminophen and 30 mg of codeine) and instructed to take a dose of analgesic once the effects of the local anaesthetic started to wear off and one dose every 3 1/2-4 hours thereafter if they continued to feel pain. This is the dose routinely given after minor oral surgery in the oral surgery clinic of the School of Dentistry of the University of Western Ontario.

All subjects received capsule(s) which appeared identical to the capsule(s) they had received during the experimental session. In reality however, all subjects received a potent analgesic and the experimenter was aware of that fact. Thus, subjects in the lo-expectancy cells again received a single white capsule which was referred to only as an "analgesic enhancer" but which contained 300 mg of acetaminophen and 30 mg of codeine. Subjects in the high expectancy cells were told they were receiving a white "analgesic enhancer" (containing 300 mg of powdered milk) and a red & white analgesic which contained 300 mg of acetaminophen and 30 mg of codeine.

After receiving analgesic instructions, all subjects completed the post-surgery questionnaire (APPENDIX E) and were instructed on how to complete the post-surgery home questionnaire (APPENDIX H). All subjects returned one week after surgery to remove sutures and to hand in questionnaires.

Forty-five additional subjects participated only in the surgery session to act as controls for the sixty subjects who participated in the experimental phase. Refer to Figure 4 A&B for a full description of the study design. Fifteen of these subjects acted as controls for the lo-expectancy cells. These subjects received a white capsule which was referred to as an "analgesic enhancer" - composed of sodium calcium and

plant extracts. Subjects were told that when given with an analgesic, this medication would help the body to absorb the analgesic more quickly and more efficiently. In fact, the pill contained 300 mg of acetaminophen and 30 mg of codeine—the pharmacological analgesic equivalent of Tylenol<sup>®</sup>3. Another fifteen subjects acted as controls for the high expectancy cells. These subjects expected to receive and received a combination of a red & white analgesic (300 mg of acetaminophen and 30 mg of codeine) and a white analgesic enhancer (300 mg of powdered milk) presented as medication which helps the body absorb pain medication more quickly and more effectively. The remaining fifteen subjects acted as an "unaltered expectancy control group". These subjects received twelve McNeil Consumer Product Tylenol<sup>®</sup>3 which contained 300 mg of acetaminophen, 30 mg of codeine and 15 mg of caffeine.

The thirty subjects who acted as hi- and lo-expectancy controls read the letter of explanation for control subjects (APPENDIX K) and completed the consent form (APPENDIX K) for control subjects. They also completed the following questionnaires before surgery: 1) past-experience questionnaire (APPENDIX A); 2) State and Trait Anxiety Scale (APPENDIX C); 3) Tellegen Absorption Questionnaire. These thirty subjects also rated on 150 mm VAS their anxiety, expectations for pain and unpleasantness during surgery and their expectation for pain after surgery (APPENDIX F). The fifteen subjects who acted as the unaltered expectancy controls did not complete any questionnaires before surgery.<sup>6</sup>

At the completion of surgery, all forty-five control subjects received analgesic

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<sup>6</sup> The subjects in this group were individuals who required immediate surgery. Thus, these individuals did not anticipate bone removal for an extended period of time prior to surgery. Unlike all other subjects, the subjects who participated in the unaltered expectancy control group did not have their surgical fees waived. Receiving twelve free Tylenol<sup>®</sup>3 was their only compensation for completing the post surgery questionnaires.

instructions and completed the post-surgery questionnaire (APPENDIX G) and were instructed on how to complete the post-surgery home questionnaire (APPENDIX H). All subjects returned one week after surgery to remove sutures and to return questionnaires.

Previous studies (Price and Harkins, 1987) have reported standard deviations of about 21 with VAS ratings of thermal stimuli. If one is interested in detecting true effect sized of 1.5 or greater with a power of .90, the same size for each group should be 20, whereas detecting effect sizes of 1.5 with a power of .70 requires a sample size of 15 subjects per group.

## CHAPTER FIVE

### Results

#### Characteristics of the Sample

Data on several demographic and experiential variables such as age, sex, rating of difficulty of past-experience at the dentist, average quantity of analgesics taken per month, rating of effectiveness of analgesics in general, absorption scores, trait anxiety measures, dentist's ratings of difficulty of procedure and expected post-surgical pain were collected to assess their influence on perceived analgesic efficacy. Because subjects were randomly assigned to the seven groups, there was no control to ensure group equality on those variables. A series of One-Way Analyses of Variance (ANOVA) performed on the continuous variables and Chi-Square Tests performed on the categorical variables revealed group differences in subjects' past-experience at the dentist and the number of teeth extracted (see Table 1).

Post-hoc tests for group differences on the two variables which yielded significant main effects — past-experience at the dentist and number of teeth extracted — revealed no significant group differences. Despite the fact that group differences were not found, two additional contrasts were completed in order to maximize the certainty with which experimental results are attributable to experimental manipulations rather than to pre-existing factors. The two orthogonal contrasts computed on past-experience at the dentist were: 1) contrast between the groups who received an analgesic during the experimental session ( $M=2.37$ ;  $sd=.73$ ) and those who received a placebo ( $M = 1.63$ ;  $sd=1.64$ ); and 2) contrast between the groups who received hi-expectancy instructions during the experimental session ( $M=2.10$ ;  $sd=.69$ ) and those

TABLE 1. Mean Values for Characteristics of the sample with respective F-ratios

Variables	F-ratio	Lo- Expectancy Control	Hi- Expectancy Control	Lo- Expectancy Analgesic	Lo- Expectancy Placebo	Hi- Expectancy Analgesic	Hi- Expectancy Placebo	Tylenol 3 Control
Age of participants	<b>.94</b>	25.60 (6.16)	25.40 (5.94)	23.93 (4.43)	23.80 (5.43)	24.33 (4.41)	22.20 (2.04)	No data
# of analgesics per month	<b>.52</b>	2.53 (5.15)	2.33 (3.11)	1.93 (3.75)	3.60 (5.75)	3.27 (3.49)	1.60 (2.53)	No data
Rating of effectiveness of analgesics	<b>1.60</b>	81.47 (38.16)	99.80 (33.62)	75.53 (38.39)	107.20 (19.00)	95.60 (40.59)	91.53 (40.54)	No data
Past-experience at dentist	<b>3.16**</b>	1.93 (.92)	2.23 (.83)	2.13 (.83)	1.67 (.90)	2.60 (.63)	1.60 (.74)	No data
Absorption Scores	<b>.36</b>	22.60 (5.94)	22.40 (5.99)	21.20 (6.73)	20.80 (5.02)	21.00 (4.77)	20.27 (6.97)	No data
Trait anxiety (STAI)	<b>1.49</b>	36.60 (7.94)	39.53 (6.49)	42.00 (6.62)	39.20 (6.05)	37.00 (6.48)	35.40 (10.53)	No data
Oral surgeon's evaluation of difficulty	<b>.77</b>	90.93 (28.19)	88.20 (31.29)	74.27 (27.21)	81.60 (30.97)	92.67 (28.09)	90.83 (23.69)	88.20 (29.51)
# of extractions	<b>2.88**</b>	1.47 (.64)	1.60 (.51)	1.40 (.51)	1.53 (.52)	2.07 (.70)	1.80 (.72)	1.33 (.49)
Oral surgeon's rating of expected post-op pain	<b>.42</b>	84.47 (25.68)	79.60 (22.46)	73.93 (27.25)	74.47 (26.25)	81.73 (28.86)	79.08 (23.05)	72.40 (30.76)

N B Numbers in parentheses are standard deviations

who received lo-expectancy instructions ( $M = 1.89$ ;  $sd = .87$ ). The first contrast revealed that those who received an analgesic during the experimental session had significantly more negative past-experiences at the dentist than subjects who received a placebo ( $t = 3.63$ ;  $p < .001$ ). Thus, where appropriate, past experience at the dentist was entered as a covariate in subsequent analyses. The second contrast between those who received hi and those who received lo expectancy instructions did not achieve statistical significance.

Post-Hoc Tukey-HSD tests on the number of teeth extracted revealed that subjects in the lo-expectancy analgesic group ( $M = 1.40$ ;  $sd = .51$ ) had significantly ( $p < .05$ ) fewer teeth extracted than those in the hi-expectancy analgesic group. This result would have the net effect of making the surgery more difficult for the hi-expectancy groups than for the lo-expectancy group. This will have a conservative effect on the statistical tests aimed at looking for group differences. However, the oral surgeons' rating of difficulty associated with the extraction(s) and the oral surgeons' rating of expected post-surgical pain did not differ significantly across groups.

### **Organization of Results**

The results are organized into three main sections: Experimental session results; surgical session results; and post-surgical session results. The tests of hypotheses are in the same order as the respective statements of hypothesis in the introduction. The questions raised in the presentation of some hypotheses are also addressed under the corresponding hypothesis heading. At the end of the first two sections, experimental session and surgical session, the data are subjected to regression analyses to further examine the relationships among the variables collected in this study

and to generate hypotheses for further research. A short summary of the findings is included after each test of hypotheses.

### **Experimental Session Results**

Sixty subjects participated in the experimental session. They provided baseline ratings of the intensity and the unpleasantness of painful heat stimuli and were then subjected to one of four experimental conditions: 1) expect a placebo/receive a placebo (lo-expectancy placebo); 2) expect a placebo/receive an analgesic (lo-expectancy analgesic); 3) expect an analgesic/receive a placebo (hi-expectancy placebo); and 4) expect an analgesic/receive an analgesic (hi-expectancy analgesic). Subjects' appraisal of the pill's or pills' analgesic effectiveness was obtained both before and after they rated the painful stimuli a second time.

#### **Subjective ratings of expectancy, anxiety and side-effects (Hypothesis 1).**

To test that hi-expectancy instructions produced greater expectations of analgesic efficacy than lo-expectancy instructions, subjects' ratings of expectation for analgesic efficacy immediately after administration of the pill(s) were subjected to a OneWay ANOVA. The analysis yielded a significant univariate main effect ( $F=3.17$ ;  $p=.03$ ). Two orthogonal contrasts were computed: 1) hi-expectancy versus lo-expectancy groups; and 2) combination of the groups who received an analgesic versus the groups who received a placebo. The first contrast was significant ( $t=-3.03$ ;  $p=.004$ ) indicating that subjects who received hi-expectancy instructions ( $M=85.66$ ;  $sd=37.3$ ) rated significantly greater anticipated analgesic effectiveness than those who received lo-expectancy instructions ( $M=55.74$ ;  $sd=38.82$ ). These differences between hi- and lo-expectancy groups were still present ( $t=-2.34$ ;  $p=.02$ ) after subjects had first hand

experience with the analgesic (or placebo) effects of drug (ie. after rating the painful stimuli a second time). The second contrast (analgesic vs. placebo) did not achieve statistical significance.

In addition, subjects who had received hi-expectancy instructions experienced significantly ( $t=-2.44$ ;  $p=.02$ ) greater initial anxiety ( $M=60.36$ ;  $sd=56.71$ ) than did subjects who had received lo-expectancy instructions ( $M=31.6$ ;  $sd=38.49$ ). However, hi-expectancy experimental subjects rated themselves as significantly more anxious (trait anxiety) than the lo-expectancy experimental subjects ( $t=2.21$ ;  $p=.03$ ). When trait anxiety is taken as a covariate, the difference in initial anxiety reported by the hi- and lo-expectancy subjects remains. Similarly, when past experience at the dentist is taken as a covariate, the difference in initial anxiety remains. Thus, trait anxiety differences between the hi and lo-expectancy subjects and in past experience at the dentist do not account for the group difference in reported anxiety when subjects received the pill(s).

A covariate analysis of variance of post-anxiety measures with initial anxiety as a covariate yielded significant covariate effects ( $F_{(1,55)}=15.76$ ;  $p<.000$ ) and no main effect for group ( $F_{(3,55)}=.56$ ;  $p<.64$ ). Thus, when initial anxiety levels are taken into account, post anxiety measures do not differ significantly across groups. Figure 5 illustrates anxiety scores for all four experimental groups.

In addition to the differences obtained in subjective reports of expectation for pain relief and anxiety between the hi-expectancy and lo-expectancy groups, the groups also differed significantly in the number of side-effects they reported. Two *a priori* orthogonal contrasts were computed to examine the difference in number of side effects



reported by: 1) hi- vs lo-expectancy groups; and 2) analgesic vs placebo groups. The first contrast revealed that subjects in hi-expectancy groups reported a significantly ( $t=.13$ ;  $p=.05$ ) greater number of side effects ( $M=3.00$ ;  $sd=2.39$ ) than those in the lo-expectancy groups ( $M=.90$ ;  $sd=2.14$ ). The second contrast between the analgesic and placebo groups did not reach statistical significance.

Table 2 presents the proportion of subjects who reported more than one side-effect per group<sup>7</sup>. The Chi-Square test for number of side-effects was significant ( $\chi^2_{(1)}=16.4$ ;  $p<.005$ ) and this result apparently is due to the greater proportion of subjects reporting side-effects in the hi-expectancy conditions.

**TABLE 2**                      **Number of Subjects Reporting More than 1 Side Effect**

Subject Receives	Subject Expects	
	Lo	Hi
Placebo	7/15	10/15
Analgesic	6/15	12/15

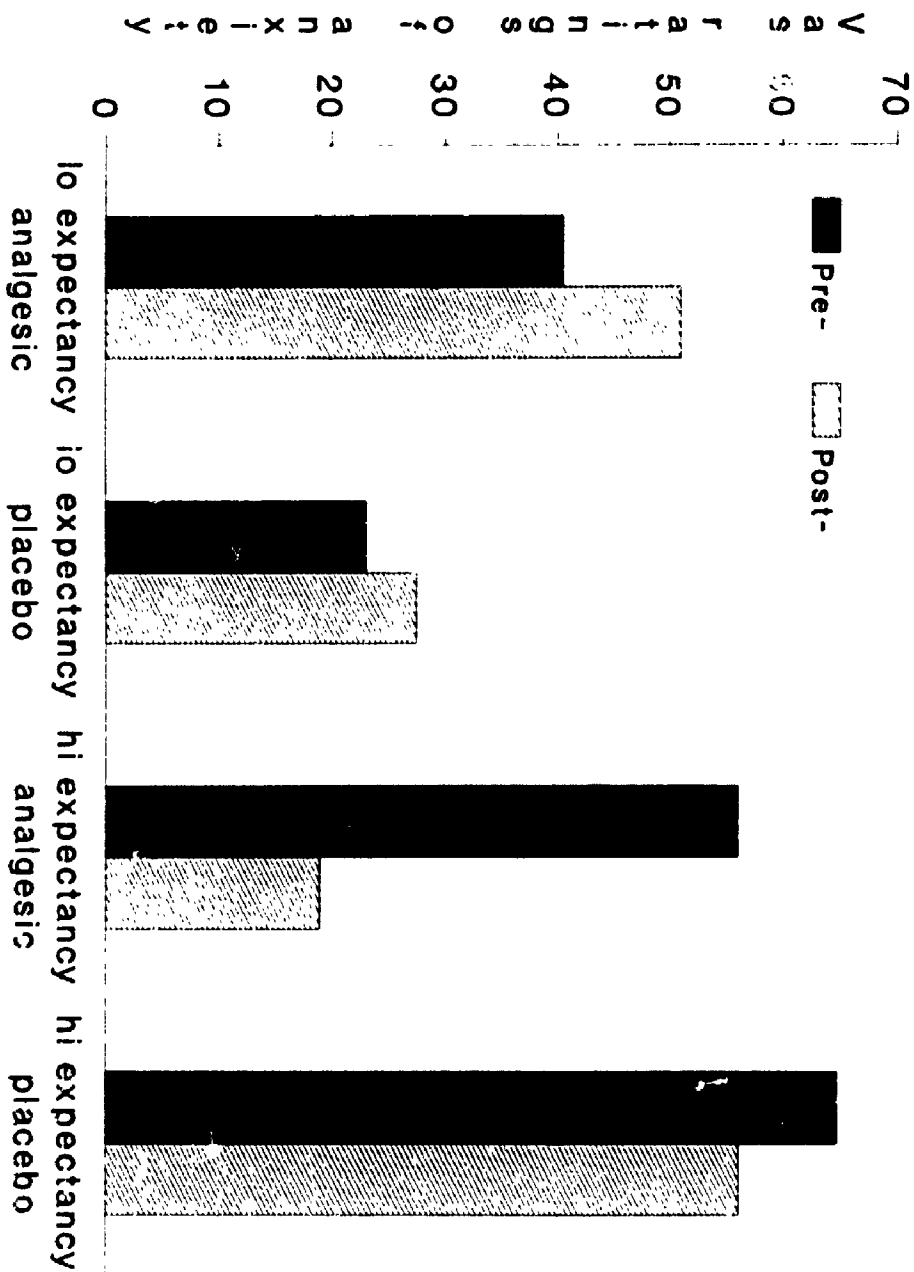
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<sup>7</sup>Only subjects who reported more than one side effect were considered because, regardless of group assignment, most subjects endorsed sleepiness as a side effect.

**Figure 5**

Visual analogue scale ratings of anxiety as plotted for each experimental group. Solid bars represent ratings of anxiety before receiving the pill(s) while hatch bars represent anxiety ratings 45 minutes after having received the pill(s).

Figure 5 Mean Pre- and Post-Treatment Anxiety Ratings by Experimental Group



Two important observations must be made. First, although subjects in the lo-expectancy conditions were told that they would receive a seemingly impotent drug, they were still comfortable in reporting side-effects to the medication; thus, one can surmise that they would also be willing to report pain reduction if they experienced it. These results are congruent with the pilot study outcome. Second, in this study, it appears that expectancy instructions were a more important determinant of the number of side effects reported by subjects than was the presence or absence of an active pharmacological component in the pill(s).

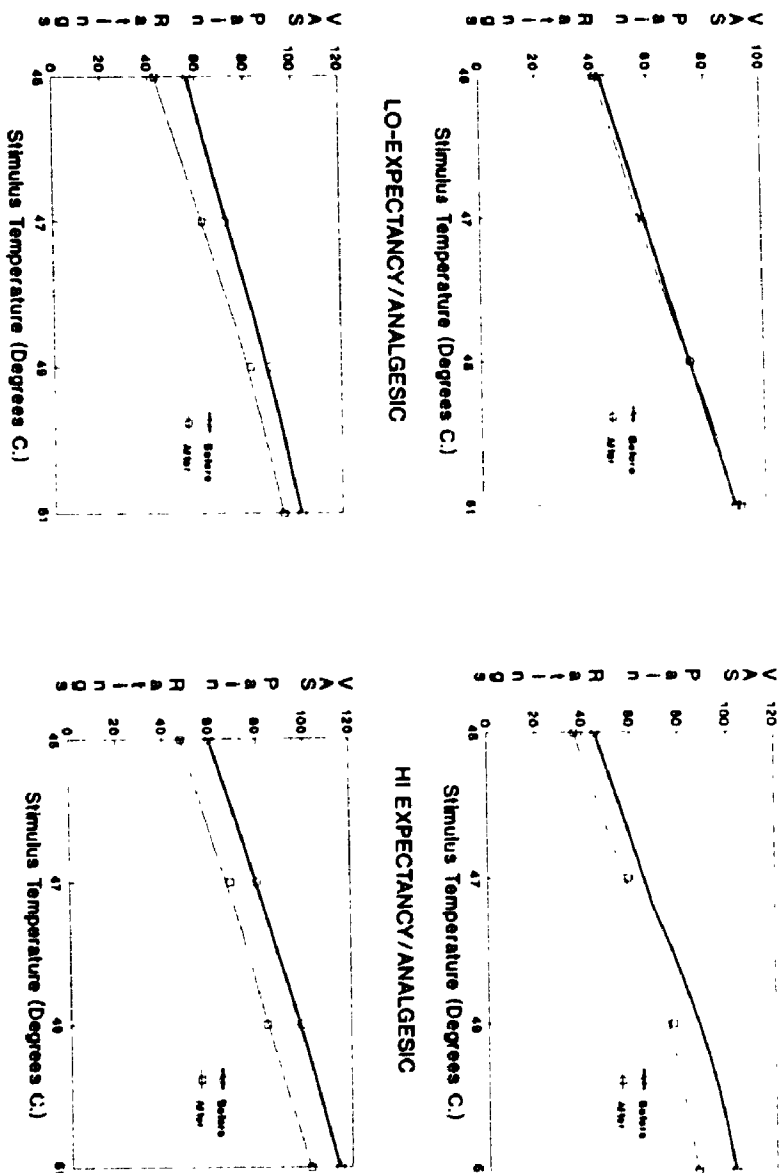
*In summary, expectancy instructions successfully produced higher expectation of analgesic efficacy in the hi-expectancy groups than in the lo-expectancy groups. These differences persisted after subjects had experienced (or had not experienced) the pharmacological effects of the pill(s). Contrary to our hypothesis, hi-expectancy subjects experienced significantly greater initial anxiety than did lo-expectancy subjects. Although visual inspection of the anxiety data (Figure 5) suggests reductions in anxiety for the hi-expectancy subjects and increases in anxiety for lo-expectancy subjects, these differences were not statistically significant. Finally, the results also suggest that in this study, the expectancy component of the drug-giving ritual was a more important determinant of whether individuals reported side-effects and how many side-effects they reported than was the presence or absence of an active pharmacological component in the drug.*

**Subjective Ratings of Pain (Hypothesis 2).** Pre- and post-group means of pain and unpleasantness ratings of the noxious heat stimuli are presented in Figures 6 and 7.

### Figure 6

Mean VAS intensity ratings for each group before and after receiving the pill(s) are plotted as a function of stimulus intensity expressed in C. Each open circle represents the mean baseline rating for 15 subjects while each open square represents the mean for the same subjects after treatment.

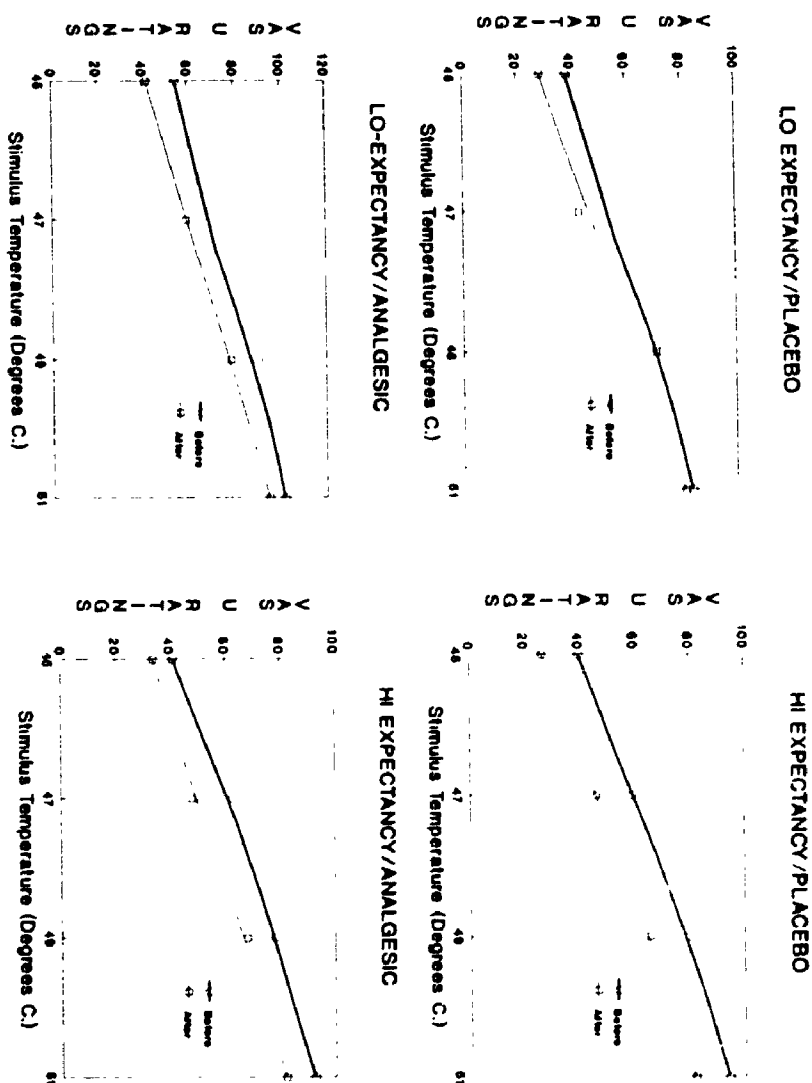
**Figure 6**  
**Group Pain Ratings Before and After Treatment**  
 LO EXPECTANCY/PLACEBO  
 HI EXPECTANCY/PLACEBO



### **Figure 7**

Mean VAS unpleasantness ratings for each group before and after receiving the pill(s) are plotted as a function of stimulus intensity expressed in C. Each open circle represents the mean baseline ratings for 15 subjects while each open square represents the mean for the same subjects after treatment.

Figure 7  
Group Unpleasantness Ratings before and after Treatment





Hypothesis 2 states that as a group (regardless of whether they receive a drug or a placebo), subjects who receive hi-expectancy instructions will experience greater pain/unpleasantness relief than subjects who receive lo-expectancy instructions. The hypothesis will be examined first for the pain intensity data and then for the unpleasantness data.

***Pain Intensity.*** A 2x2 between-subjects multivariate analysis of covariance was performed on the four dependent measures: post pain ratings at 45°, 47°, 49°, and 51°C. Pre-pain ratings at the four temperatures were entered as covariates. Independent variables were expectations (hi and lo) and drug (analgesic and placebo). Analyses were done using SPSS MANOVA. Results of evaluation of assumptions of normality, linearity and multicollinearity were not satisfactory, thus, the Greenhouse-Geisser Epsilon adjustment was performed on the degrees of freedom of the within subject effects.

After statistically adjusting for pre-treatment pain rating levels, the analysis yielded a significant main effect for expectancy ( $F_{(1, 55)}=4.77, p<.033$ ), and for intensity ( $F_{(1, 69)}=4.0; p<.04$ ). See Table 3 for summary statistics of effects. The significant effect for expectancy indicates that when compared to subjects who received lo-expectancy instructions, hi-expectancy subjects reported significantly lower levels of pain intensity after receiving the pills. Table 4 depicts the predicted means for each experimental cell after taking out the effects of the covariate.

**Table 3. Summary statistics for 2(drug)x2(expectancy)x4(post-pain intensity) within subject design MANCOVA procedure with pre-pain ratings as the covariates**

<b>Between Subjects Effects</b>	<b>df</b>	<b>F ratio</b>	<b>p-value</b>	
Regression	1	316.01	.000	
Expectancy	1	4.77	.033	
Drug	1	2.26	.139	
Expectancy x Drug	1	1.85	.179	
Within	55			
<b>Within Subjects Effects</b>	<b>df</b>	<b>F ratio</b>	<b>p-value</b>	<b>adjusted p*</b>
Regression	1	105.57	.000	.001
Intensity	3	4.00	.009	.04
Expectancy x Intensity	3	1.70	.168	
Drug x Intensity	3	.37	.777	
Expectancy x drug x intensity	3	.76	.519	

\* Greenhouse-Geisser Adjustment

TABLE 4

Predicted Means for Average Post Pain Intensity Ratings once  
the Effects of Pre-Pain Intensity Ratings Have Been Removed.

Subject Receives	Subject Expects		Mean
	Lo	Hi	
Placebo	150.73	132.95	141.84
Analgesic	136.26	132.00	134.13
Mean	143.50	132.48	

**Pain Unpleasantness.** As with pain intensity data, the pain unpleasantness data were subjected to a 2x2 between subjects multivariate analysis of covariance followed by a OneWay Analysis of covariance on average post-unpleasantness ratings using average pre-unpleasantness ratings as a covariate. The only significant main effect was obtained for intensity ( $F_{(1, 69)}=6.44$ ;  $p<.03$ ) indicating that subjects rated the lower intensity stimuli as less unpleasant than hi-intensity stimuli.

***Pattern of Analgesia Obtained in Different Groups (Hypothesis 2, question i).***

In order to verify that the subjective responses obtained in this study are comparable to those of other studies done with thermal stimulation, the relationships between temperature intensity and VAS reports of sensory intensity and unpleasantness were made linear by natural logarithmic transformation (Stevens, 1975). The transformed values were then analyzed using multiple regression analyses. The results of the multiple regression allowed for the description of power functions ( $\psi = 10^{\text{intercept}^k} \times \text{stimulus intensity slope}$ ) between stimulus intensity (S) and VAS sensory intensity ratings ( $\psi$ ) or VAS unpleasantness ratings (y). In their logarithmic form, the functions represent a ratio scale

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<sup>8</sup> Refers to properties of the linear regression  $B_0$  &  $B_1$ . Price (1988, p. 27) states that "The ratio properties of judgements...are intimately associated with power law, which states that perceived magnitude is a power function of stimulus magnitude," expressing the relationships as follows:

$$\psi = kS^n$$

where  $\psi$  = perceived stimulus intensity  
 $k$  = proportionality constant  
 $S$  = stimulus intensity  
 $n$  = exponent (constant) of the power function

The linear logarithmic transformation of this equation is:  $\psi = \log k + n \log S$  where y-int =  $\log k$ , slope =  $n$

(Stevens, 1975). This procedure yielded one power function of VAS intensity reports to stimulus intensity and one power function of VAS unpleasantness reports to stimulus intensity before and after receiving the pill(s) for each subject.

In line with Price's (1988) conclusions, it is expected that the subjects who received codeine will experience reductions in different intensities of pain sensations by a nearly constant numerical — that is, low intensity pains will be reduced to a greater extent than sharp intense pains. In other words, pain ratings for subjects in the two analgesic groups should show significantly greater changes in slope and in y-intercept than for the two placebo groups.

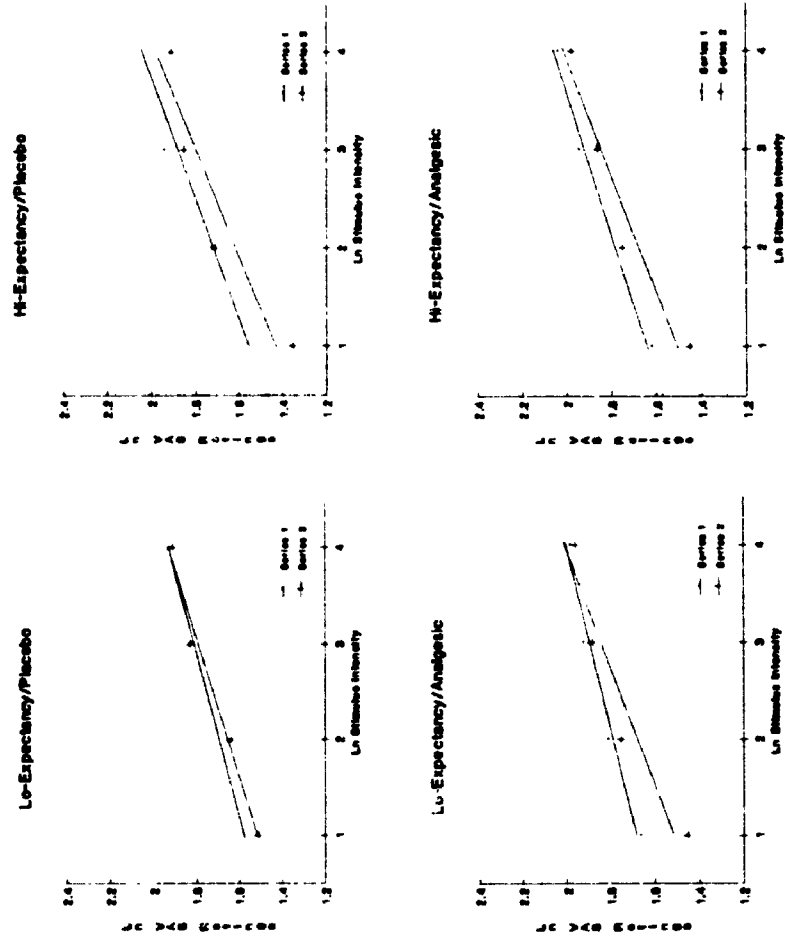
Figures 8 and 9 show graphs of the linear representation of the underlying power functions relating subjective reports of sensory intensity and unpleasantness (VAS ratings) to stimulus intensity. Visually inspection of the figures supports the findings that in general, hi-expectancy subjects experienced significantly more analgesia than lo-expectancy subjects. However, visual inspection of the figures does not suggest characteristically distinct patterns of analgesia for the drug groups when compared to the placebo groups.

To test whether there are group differences in the characteristics of the power functions, a series of 2 (expectancy level) x 2 (drug received) analyses of covariance (characteristics of the baseline linear functions as covariates) performed on the slope and y-intercept data yielded no significant main effect for either sensory intensity nor unpleasantness, thus suggesting no significant group differences in slope or y-intercept.

### **Figure 8**

Mean ln VAS intensity ratings for each group before and after receiving the pill(s) are plotted as a function of ln stimulus intensity. Each dot represents the mean baseline rating for 15 subjects while each cross represents the mean for the same subjects after treatment.

**Figure 8**  
**Linear Transformation of Group Pain Ratings**  
**Before and after Treatment**

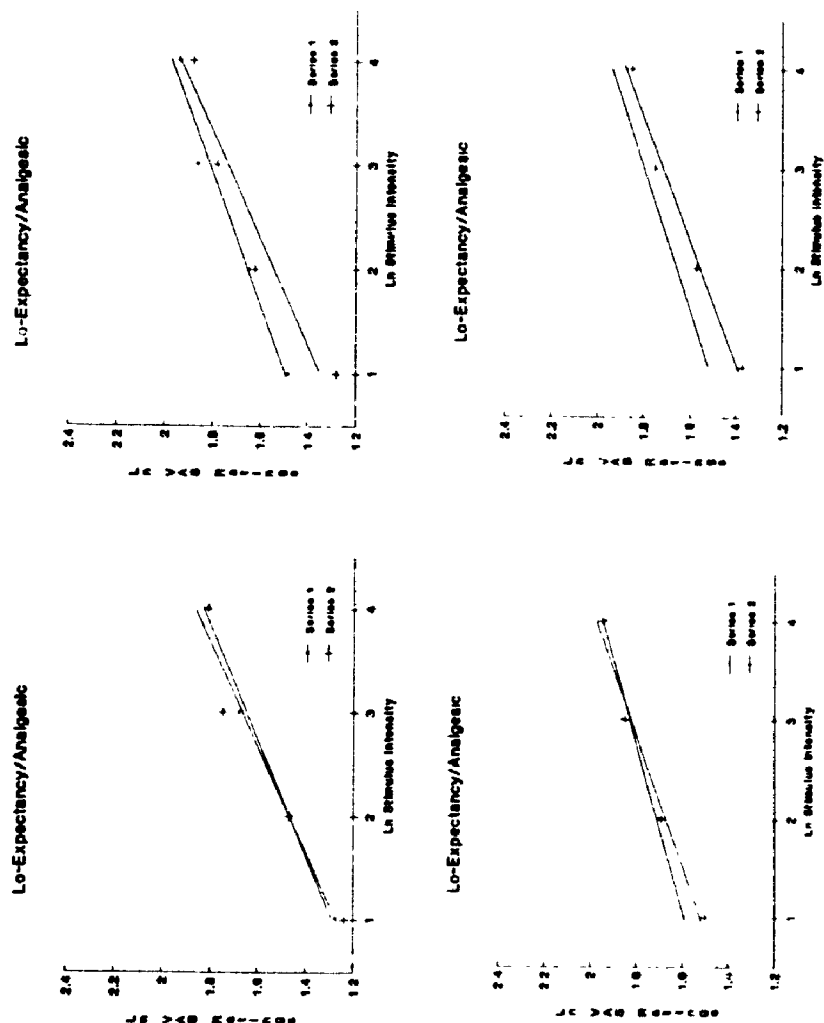


### **Figure 9**

Mean ln VAS unpleasantness ratings for each group before and after receiving the pill(s) are plotted as a function of ln stimulus intensity. Each dot represents the mean baseline rating for 15 subjects while each cross represents the mean for the same subjects after treatment.



Figure 9  
 Linear Transformed Group Unpleasantness Ratings  
 Before and After Treatment



***Pain Intensity vs Unpleasantness Ratings (Hypothesis 2; Question ii).*** To test Gracely, McGrath and Dubner's (1979) hypothesis that placebo acts primarily by reducing the unpleasantness rather than the intensity component of the pain experience, multivariate analysis of covariance was performed on the two ratings of the sensation (intensity and unpleasantness). Pre-treatment pain intensity and unpleasantness ratings were entered as covariates. The independent variable was group assignment. After statistically adjusting for pre-treatment pain and unpleasantness levels, the analysis yielded significant main effects for group ( $F_{(1, 55)} = 3.51, p < .02$ ) but no main effect for dimension nor group by dimension. This result indicates that in this study, 1) subjects did not rate the intensity component of the noxious stimuli significantly differently than they rated the unpleasantness component and, 2) the various groups did not rate these dimensions differently. Thus, the placebo group, when compared to other groups, did not report a greater reduction in unpleasantness than in intensity.

***Relationship Between Anxiety and Pain/Unpleasantness Reductions (Hypothesis 2; Question iii).*** The anxiety measures collected were: 1) STAI-trait anxiety measure collected before subjects were allocated to their treatment group; 2) VAS rating of anxiety collected immediately after group allocation; and 3) SSAI-state anxiety measure also collected immediately after group allocation.

A median split was computed for each anxiety measure, thus, separating hi- and lo-anxiety subjects. For the STAI, the median was 37; for VAS, the median was 29 and for SSAI, the median was 31. Based on past research studies with placebos in pain research, these three measures of anxiety are expected to be related to the extent

of pain relief reported by subjects. Pre-pain intensity ratings were entered as covariates. The post-pain intensity ratings (with pre-intensity ratings partialled out), served as the dependent variable. The independent variable for each analysis was the level of anxiety on each of the three anxiety measures. The analysis of covariance, then, provides a test of the effect of anxiety levels on post-pain ratings. All three analyses yielded significant covariate main effects suggesting that pre-pain ratings are significantly related to post-pain ratings. However, there were no significant main effects for the three measures of anxiety, suggesting that anxiety levels were not significantly related to the levels of sensory-intensity reported 45 minutes after ingestion of the pill(s).

In order to test if subjects who reported high levels of anxiety also tended to report hi-levels of sensory intensity after receiving the pill(s), a count was tabulated for each cell — hi-anxiety/lo-sensory intensity; hi-anxiety/hi-sensory intensity; lo-anxiety, hi-sensory intensity; lo-anxiety/lo-sensory intensity. A median split was computed for post pain intensity ratings (with pre-pain intensity partialled out) yielding two groups—lo-sensory intensity and hi-sensory intensity. A count was tabulated for each of the three anxiety measures, Table 5. A Chi Square computed for VAS anxiety ratings ( $\chi^2=6.67$ ;  $p<.07$ ) yielded nearly significant results. Chi square computed for STAI and SSAI, was not statistically significant ( $\chi^2=2.4$ ;  $p>.05$ ).

**TABLE 5** Proportion of subjects reporting hi/lo levels of anxiety and hi/lo levels of post-treatment sensory intensity.

**a) Visual analogue scale ratings of anxiety:**

		Anxiety	
		Lo	Hi
Post-Treatment Sensory Intensity	Lo	20/60	10/60
	Hi	10/60	20/60

**b) SSAI ratings of anxiety:**

		Anxiety	
		Lo	Hi
Post-Treatment Sensory Intensity	Lo	18/60	12/60
	Hi	12/60	18/60

**c) STAI ratings of anxiety:**

		Anxiety	
		Lo	Hi
Post-Treatment Sensory Intensity	Lo	12/60	18/60
	Hi	18/60	12/60

*In summary, the hypothesis testing revealed that lower levels of sensory intensity were reported by subjects who received hi-expectancy instructions than by those who received lo-expectancy instructions. No main effects were obtained for drug, thus indicating that within the experimental pain context, the expectancy component of the drug-giving ritual was a more important determinant of reported levels of sensory intensity of noxious heat pulses than was the presence or absence of an active pharmacological component in the drug. Contrary to predictions, there were no post-treatment group differences in the ratings of unpleasantness of the noxious heat stimuli.*

*Examination of the power functions between temperature intensity and VAS reports of sensory intensity and unpleasantness did not reveal any significant main effects for either the slope or the y-intercept indicating that in this study the two different treatments (active drug or placebo) did not result in characteristically different patterns of analgesia.*

*The results of this study indicate that placebo's effect did not come about primarily by reduction in the unpleasantness of the sensation. There was a trend to suggest that subjects who experienced high levels of situational anxiety (as measured by VAS anxiety ratings), also experienced greater levels of pain (ie: less analgesia) than subjects who reported lower levels of situational anxiety.*

**Regression Approach.** A regression analysis approach was used to further clarify the relationship among pre-experimental variables and pill effects, and to generate hypotheses for future research. In order to reduce the number of variables to examine in the regression approach, the intercorrelation among pre-experimental

session variables were factor analyzed using a principal component method of extraction. The variables entered in the factor analysis were: 1) ratings of anxiety and expectancy collected immediately after taking the pill(s); 2) the level of expectancy on heart rate, blood pressure, sensitivity and anxiety produced by group assignment; 3) absorption scores.

The principal component solution accounts for 71% of the variance in the correlation matrix. Factors with an eigenvalue of more than 1 were interpreted. Inspection of the rotated factor matrix (see Table 6) suggests that Factor 1 is defined by variables related to anxiety (ANXIETY), Factor 2 is defined by variable related to subjects' perception of pill(s) potency (POTENCY), Factor 3 is defined by variables related to subjects' analgesic expectancy (EXPECTANCY) and Factor 4 is defined by absorption level (SUGGESTIBILITY).

The intercorrelation among post-experimental session data was analyzed using a principal component method of extraction. The variables dealt with pre- to post-change in pain and unpleasantness ratings as well as evaluation of the pill's(s') effectiveness. The solution accounts for 63% of the variance. Factors with eigenvalues  $> 1$  were interpreted. Inspection of the rotated factor matrix (see Table 7) suggests that Factor 1 is defined by variables related to subjects' evaluation of the general potency of the pill(s) (POTENCY), Factor 2 is defined by variables related to subjects' evaluation of analgesia related effects (PERCEIVED EFFECTIVENESS)

**Table 7 Principal Component Extraction Method of Post-Experimental Session Data**

	Factor 1 (POTENCY)	Factor 2 (PERCEIVED EFFECTIVENESS)	Factor 3 (EFFECTIVENESS)
RATING OF EFFECT ON BLOOD PRESSURE	.85	.20	-.05
RATING OF EFFECT ON HEART RATE	.75	-.29	.07
RATING OF EFFECT ON ANXIETY	-.68	.42	.15
RATING OF EFFECT ON PAIN PERCEPTION	.12	.55	-.25
# OF SIDE-EFFECTS REPORTED	.05	.74	-.08
VAS PAIN REDUCTION	.21	-.04	.78
VAS UNPLEASANTNESS REDUCTION	-.14	.01	.72

**Table 6 Principal Component Extraction Method of Pre- Experimental Session Data**

	Factor 1 (ANXIETY)	Factor 2 (POTENCY)	Factor 3 (EXPECTANCY)	Factor 4 (SUGGESTIBILITY)
STAI	.79	.09	-.32	-.07
SSAI	.85	.07	.14	-.07
VAS-ANXIETY	.57	.16	.34	.39
EXPECTED EFFECT ON BLOOD PRESSURE	.27	.72	.11	-.40
EXPECTED EFFECT ON HEART RATE	.19	.79	.03	.22
EXPECTED EFFECT ON ANXIETY LEVEL	.16	-.67	.42	.08
EXPECTED ANALGESIC EFFECT	.11	.12	.81	-.16
EXPECTANCY MANIPULATION	-.12	-.24	.75	.04
ABSORPTION SCORE	-.03	-.03	-.09	.90



and Factor 3 is defined by variables related to changes in pain and unpleasantness ratings produced by the pill(s) (EFFECTIVENESS).

Then, the variables which loaded on each factor were aggregated and subjected to regression analyses. The first regression dealt with accounting for the variance in subjects' perception of pill's(s') EFFECTIVENESS. The four factors generated for the pre-experimental data and the three factors generated for the post-experimental data were entered into a forward entry method of regression analysis<sup>9</sup>. After step 1, SUGGESTIBILITY entered in the equation,  $R^2 = .12$ ,  $F_{(1,55)} = 7.51$ ,  $p < .008$ . After step 2, PERCEIVED EFFECTIVENESS added to the prediction of EFFECTIVENESS by SUGGESTIBILITY,  $R^2 = .21$ ,  $F_{(1,48)} = 5.49$ ,  $p < .04$ . No other variables were entered.

An F-test was computed to ensure that entering all predictors into the equation would not account for a significantly greater proportion of variance. The results indicated that adding all the factors did not significantly improve the proportion of variance accounted for ( $F_{(4,48)} = 2.40$ ,  $p > .05$ ).

A similar regression approach was used with PERCEIVED EFFECTIVENESS as the dependent variable. At step 1, EXPECTANCY was entered,  $R^2 = .29$ ,  $F_{(1,55)} = 22.49$ ,  $p < .0000$ . After step 2, POST-POTENCY index added to the prediction of PERCEIVED EFFECTIVENESS by EXPECTANCY,  $R^2 = .38$ ,  $F_{(2,54)} = 16.34$ ,  $p < .0000$ . After step 3, ANXIETY was added to the equation,  $R^2 = .43$ ,  $F_{(3,53)} = 13.53$ ,  $p < .0000$ . The result of an F-test indicated that adding all the factors

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<sup>9</sup>Post-experimental session factors were also entered in the regression equation because it is plausible that although the factors are independent, they may act as moderators for each other.

to the regression equation did not significantly improve the proportion of variance accounted for ( $F_{(3,48)} = 1.31, p > .05$ ).

Finally, a similar regression approach was used with POST-POTENCY as a dependent variable. The results are presented in Table 8.

<b>Table 8 - Forward entry regression of PRE- and POST-experimental factors with POST-POTENCY as the dependent variable.</b>				
	Variable	R <sup>2</sup>	F <sub>(df)</sub>	p
STEP #1	POTENCY 1	.12	7.52 <sub>(1,55)</sub>	.008
STEP #2	EXPECTANCY	.19	6.40 <sub>(2,54)</sub>	.003
STEP #3	PERCEIVED EFFECTIVENESS	.26	6.08 <sub>(3,53)</sub>	.001
STEP #4	ANXIETY	.36	7.17 <sub>(4,52)</sub>	.0001

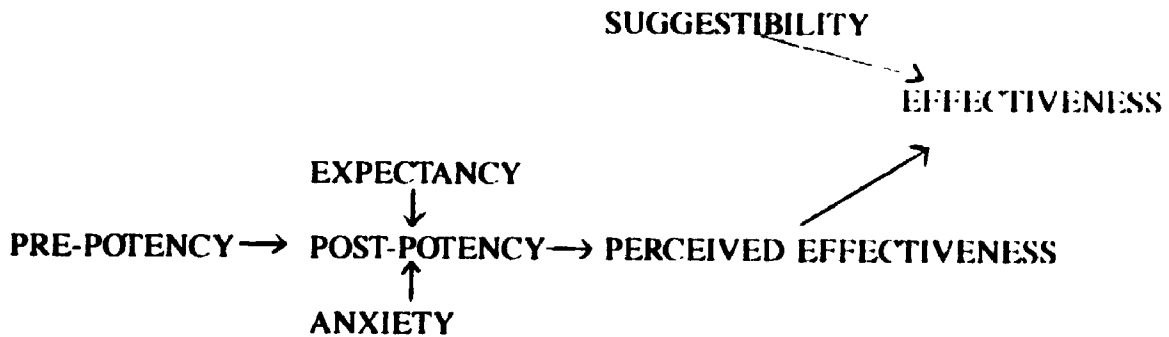
The results of an F-test indicated that adding all the factors to the regression equation did not significantly improve the proportion of variance accounted for ( $F_{(1,48)} = .53, p > .05$ ).

*In summary, the hypothesis testing approach and the regression approach to the data yielded different but complementary evidence. Expectancy was found to be more important than the presence or absence of a pharmacologically active analgesic in predicting reductions in subjective reports of sensory intensity. No significant effects were obtained for pain unpleasantness. Anxiety was found to play an important role in this effect with a greater proportion of lo-expectancy subjects experiencing high levels of pain reduction and a greater proportion of hi-anxiety subjects experiencing low*

levels of pain reduction. The regression approach yielded compelling findings. The pattern of relationships suggested by the regression approach is presented in Figure 10.

Expectancy of analgesic efficacy, anxiety levels and perception of pill's(s') effects on physiological and subjective states (heart rate, blood pressure, anxiety) all predicted perceived levels of analgesic effects (as measured by the number of side effects reported and ratings of effect on pain perception) which in turn predicted effects on subjective pain and intensity ratings of the stimuli.

**Figure 10 - Relationship among Experimental Factors**



### **Surgical Session**

Before surgery, subjects (in all conditions except Tylenol <sup>®</sup>3) completed a Spielberger State Anxiety Questionnaire (SSAI) and rated the following measures on VASs: 1) anxiety; 2) expected pain during surgery; 3) expected unpleasantness during surgery; 4) expected pain after surgery, 5) expected unpleasantness after surgery. After surgery, subjects also used VASs to rate: 1) the difficulty of the procedure; 2) pain experienced during surgery; 3) unpleasantness experienced during surgery; 4) expected effectiveness of pill(s) for relieving post-surgical pain. Subjects also rated how closely the sensations they experienced during surgery matched their expectations prior to surgery.

To determine the number of independent constructs which were measured by the variables, the intercorrelations among pre-surgical variables were factor analyzed using a principal component method of extraction. The variables entered in the factor analysis were: 1) subjective ratings of quality of past experience at the dentist's; 2) number of teeth to be extracted; 3) extent of pain/unpleasantness relief experienced in the experimental session; 4) anxiety about surgery; 5) expected pain/unpleasantness during and after surgery.

The principal component solution accounts for 65% of the variance in the correlation matrix. Factors with eigenvalues  $> 1$  were interpreted. Inspection of the rotated factor matrix (see Table 9) suggests that Factor 1 is defined by variables related to subjects' apprehension about dentists and surgery (APPREHENSION). Factor 2 is defined by variables related to anxiety (ANXIETY) and Factor 3 is defined by variables related to pain and unpleasantness relief experienced (ANALGESIC EFFECTIVENESS EXPERIENCED) in the experimental session.

Similarly, the intercorrelation among post-surgical session data was analyzed using a principal component method of extraction. The variables dealt with: 1) the oral surgeon's rating of the difficulty of the procedure and his/her expectation of the level of pain the subjects would experience after surgery; 2) subjects' ratings of pain and unpleasantness experienced during surgery; 3) subjects' ratings of the difficulty of the procedure; 4) subjects' ratings of the level of pain and unpleasantness they expect

**Table 9 Principal Component Extraction Method of Pre-Surgical Session Data for Subjects Who Participated in the Experimental Session**

Variables	FACTOR 1 (APPREHENSION)	FACTOR 2 (ANXIETY)	FACTOR 3 (ANALGESIC EFFECTIVENESS EXPERIENCED)
Pre-surgical rating of expected pain during surgery	.84	-.14	.08
Pre-surgical rating of expected unpleasantness during surgery	.73	.34	-.08
Pre-surgical rating of pain expected after surgery	.84	.19	-.03
Pre-surgical rating of unpleasantness expected after surgery	.79	.30	-.10
Number of teeth extracted	-.23	.64	-.02
SSAI	.34	.77	.01
VAS Anxiety	.36	.82	-.11
Pain relief during experimental session	-.16	-.20	.66
Unpleasantness relief during experimental session	.10	.07	.86

to experience after the effects of the local anaesthetic wears off; 5) how effective they expect the pill(s) to be at relieving pain and unpleasantness. The solution accounts for 74% of the variance. Factors with eigenvalues  $> 1$  were interpreted. Inspection of the rotated factor matrix (see Table 10) suggests that Factor 1 is defined by variables related to subjects' evaluation of the difficulty of the procedure (DIFFICULTY), Factor 2 is defined by variables related to subjects' expectation of how much pain and unpleasantness they will experience after surgery (EXPECTED POST-SURGICAL DIFFICULTY), Factor 3 is defined by variables related to subjects' expectancy of pill(s) effectiveness (EXPECTANCY) and Factor 4 is defined by variables related to oral surgeon's evaluation of the procedure (SURGEON'S EVALUATION). Factor scores were used in the analyses to test the hypotheses related to the surgical session.

**Hypothesis 3a.** It was predicted that those subjects who experienced the lowest levels of pain in the experimental session would be less anxious and apprehensive about surgery, would evaluate the surgery as having been less difficult and would anticipate greater analgesic efficacy for post-surgical pain. In order to test this hypothesis, the post VAS sensory-intensity and unpleasantness data<sup>10</sup> were divided with a median split forming two groups: one with hi levels of sensory intensity and unpleasantness and one with lo levels. Then, Analyses of Variance were computed for factor scores of ANXIETY, APPREHENSION, DIFFICULTY, EXPECTED POST-SURGICAL RELIEF. The results yielded significant group main effect for ANXIETY ( $F=12.98; p<.0007$ ) with the subjects who experienced lowest levels of pain in the

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<sup>10</sup> After the effects of pre-treatment ratings have been partialled out.

**Table 10 Principal component extraction method of post-surgical session data**

Variable	FACTOR 1 (DIFFICULTY)	FACTOR 2 (EXPECTED POST- SURGICAL DIFFICULTY)	FACTOR 3 (EXPECT- ANCY)	FACTOR 4 (SURGEON'S EVALUATION)
Pain during	.79	.09	-.02	.19
Unpleasantness during	.74	.30	-.09	.02
Rating of difficulty of procedure	.83	.04	.02	-.03
Expected pain after	.16	.93	-.02	.02
Expected unpleasantness after	.16	.93	.01	-.01
Expected analgesic efficacy	.10	-.09	.86	-.21
Expected unpleasantness relief	-.17	.06	.87	.17
Surgeon's rating of difficulty	.12	.05	-.09	.76
Surgeon's rating of pain	-.01	.04	-.05	-.81

experimental session experiencing less anxiety about surgery ( $M=63.59$ ;  $SD=18.66$ ) than the subjects who experienced the highest level of pain ( $M=83.02$ ;  $SD=18.99$ ), thus suggesting that experience of low levels of pain sensitivity in the experimental session was related to lower levels of anxiety before surgery.

Group Main effects for APPREHENSION ( $F=4.18$ ;  $p<.05$ ) suggest that subjects who experienced the lowest levels of pain in the experimental session also experienced less apprehension about surgery ( $M=89.54$ ;  $SD=26.92$ ) while those experiencing high levels of pain were more apprehensive ( $M=102.04$ ;  $SD=18.38$ ). The two groups did not differ in how difficult they perceived surgery to be or in their level of expectation of post-surgical pain relief.

**Hypothesis 3b.** It was expected that when compared to control subjects, experimental subjects would report greater levels of ANXIETY and APPREHENSION. It was also expected that when compared to subjects who received lo-expectancy instructions, hi-expectancy instruction subjects would: 1) appraise the surgery as having been less difficult (DIFFICULTY); 2) expect less post-surgical pain and unpleasantness (EXPECTED POST-SURGICAL DIFFICULTY); and 3) have greater expectancy of analgesic efficacy (EXPECTANCY).

The surgical factors were subjected to OneWay Analyses of Variance. Then, four contrasts were computed: 1) control group vs. experimental groups; 2) hi-expectancy experimental groups vs. lo-expectancy experimental groups; 3) experimental groups who received an analgesic during the experimental session vs. groups who received a placebo; 4) hi-expectancy control group vs. lo-expectancy control



group. Table 11 shows that the Analysis of Variance revealed significant main effects for groups for ANXIETY, APPREHENSION and EXPECTANCY.

**Anxiety.** Post-hoc contrasts yielded differences in ANXIETY between the control groups ( $M=48.64$ ;  $SD=15.21$ ) and the experimental groups ( $M=57.16$ ;  $SD=13.74$ ) with the control groups being significantly ( $t=-2.88$ ;  $p<.005$ ) less anxious than the experimental group. Apparently, taking part in the experimental phase of the study increase anxiety about surgery. Contrasts also yielded significant differences in ANXIETY ( $t=-3.13$ ;  $p<.005$ ) between the hi-expectancy ( $M=62.25$ ;  $SD=13.36$ ) and the lo-expectancy experimental subjects ( $M=52.06$ ;  $SD=14.12$ ), thus indicating that having received hi-expectancy instructions seems to be related to heightened anxiety levels before surgery. No differences were obtained between those who received a placebo and those who received an active drug nor between hi-expectancy control and lo-expectancy control subjects.

**Apprehension.** Post-hoc contrasts yielded differences in APPREHENSION between the control groups ( $M=64.68$ ;  $SD=34.96$ ) and the experimental groups ( $M=88.39$ ;  $SD=28.63$ ) with subjects in the control groups being significantly less apprehensive ( $t=-4.17$ ;  $p<.005$ ) than subjects in the experimental groups. No other contrasts achieved significance.

**Expectancy.** Post-hoc contrasts revealed differences in expectancy of post-surgical analgesic efficacy between the control groups ( $M=96.82$ ;  $SD=26.02$ ) and the experimental groups ( $M=75.69$ ;  $SD=23.76$ ) with the control groups expecting significantly more pain relief ( $t=-3.74$ ;  $p<.000$ ) than the experimental groups. The

**Table 11 Analyses of Variance on Surgical Session Factor of Anxiety and Expected Sensations During and After Surgery -- with Post-Hoc Contrasts**

	F-Ratio	CONTRASTS (t values)			
		Control vs. Experimental	Hi-Expectancy Experimental vs. Lo-Expectancy Experimental	Analgesic vs. Placebo	Hi-Expectancy Control vs. Lo-Expectancy Control
ANXIETY	3.85**	-2.88**	-3.13**	.99	-.05
APPREHENSION	5.59***	-4.17***	-2.23	1.90	-.63
DIFFICULTY	1.21	-1.35	.31	-1.02	.77
EXPECTANCY	5.74***	-3.67***	2.59*	-.17	2.78*
EXPECTED POST- SURGICAL DIFFICULTY	1.21	-2.25	-.91	-.21	-.23

Bonferroni = .05/5 = .01

\*  $p \leq .01$

\*\*  $p \leq .005$

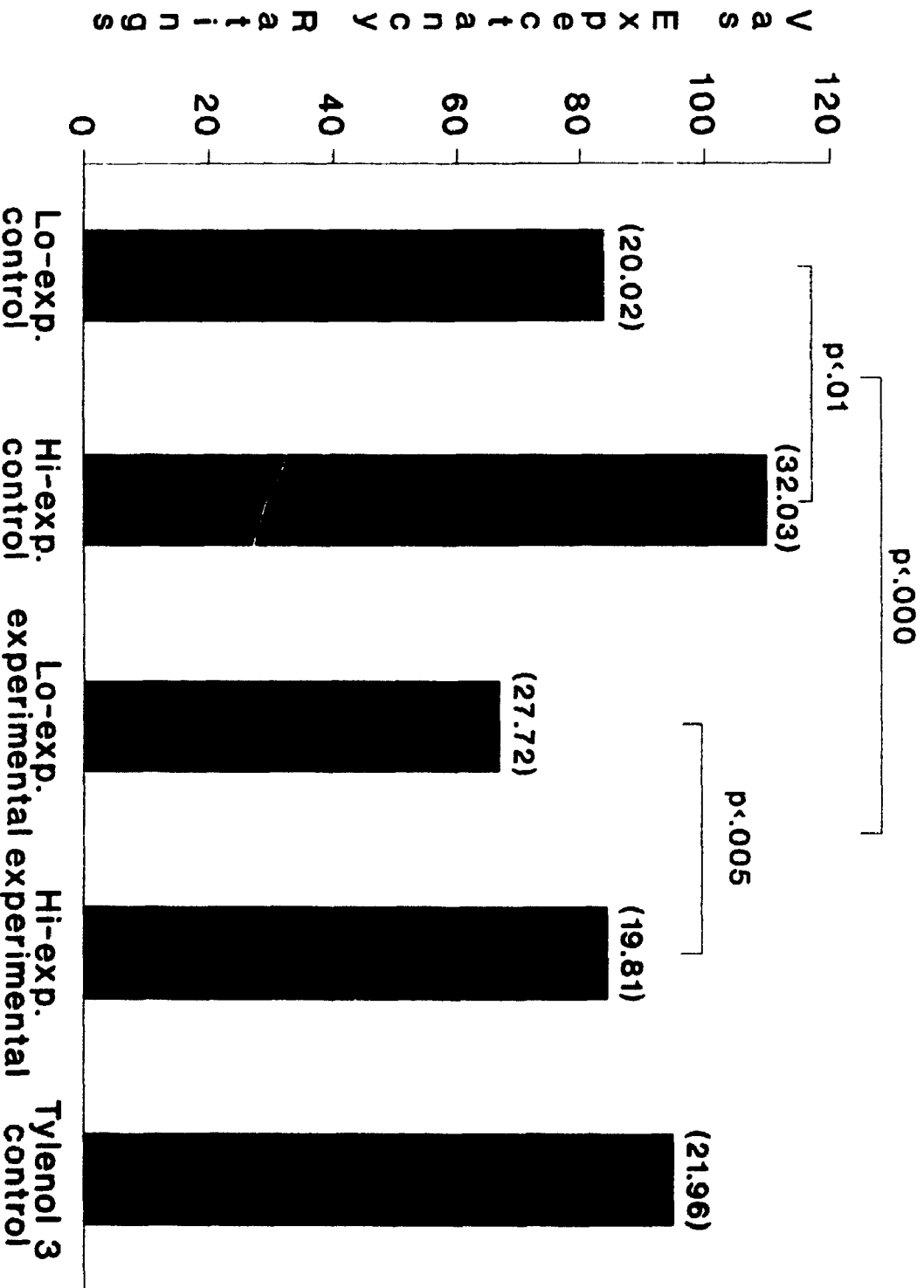
\*\*\*  $p \leq .0005$

experimental groups had significantly different levels of expectancy with hi-expectancy experimental subjects exhibiting significantly greater expectancies of analgesic efficacy than lo-expectancy experimental subjects. No differences were obtained between those who received a drug and those who received a placebo in the experimental session. Figure 11 depicts the differences among groups. Because there were no differences between subjects who received a drug and those who received a placebo, the experimental groups were combined by expectancy levels.

Since pre experiment group differences existed in subjects' ratings of the difficulty of their past experiences at the dentist's, the same analyses were computed using past experiences as a covariate. The analyses yielded no significant covariate effects while the group main effects and contrasts remained.

*In summary, the hypothesis testing revealed that subjects who, 45 minutes after receiving the pills, reported the lowest levels of pain (regardless of group assignment) tended to be less anxious and less apprehensive about surgery. On the other hand, hi-expectancy subjects were more anxious and apprehensive about surgery than were lo-expectancy subjects. This is somewhat surprising since one would expect that hi-expectancy subjects would be the ones to experience the lowest levels of pain 45 minutes after receiving the pills. In order to clarify the relationships among expectancy, analgesia experienced in the experimental session and subsequent anxiety about surgery, a 2 (levels of reported pain) x 2 (levels of expectancy) Anova was computed for the ANXIETY factor. The results revealed significant effects for pain levels ( $F=5.34$ ,  $p<.025$ ) and expectancy levels ( $3.72$ ;  $p<.05$ ) but no significant*

Figure 11 Post-Surgical Ratings of Expectancy for Analgesic Efficacy



N.B. Numbers above bars are standard deviations.

*effects for interaction ( $F=1.15$ ;  $p<.28$ ), thus suggesting that the relationships among the level of pain experienced in the experimental session, expectancy and pre-surgical anxiety are mediated by other factors.*

*Experience of lower pain perception in the experimental session did not directly result in changes in perception of the difficulty of the procedure or levels of expectation of post-surgical pain relief. In addition, the results indicated that taking part in the experimental phase of the study had the net effect of producing heightened levels of anxiety and apprehension about surgery as well as reducing the levels of overall expectancy for analgesic efficacy.*

**Regression Approach.** A regression analysis approach was used to clarify the relationship among pre-surgical factors and post-surgical factors and to generate hypotheses for future research.

The first regression dealt with accounting for the variance in subjects' perception of surgical difficulty (DIFFICULTY). The two factors generated from the pre-surgical variables<sup>11</sup> and the four factors generated from the post-surgical variables were entered into a forward entry method regression analysis. Only one factor, EXPECTED POST-SURGICAL DIFFICULTY was entered in the equation,  $R^2 = .08$ ,  $F_{(1,79)} = 7.26$ ,  $p < .009$ . Entering all the variables into another regression equation yielded an  $R^2 = .16$  which did not account for a significantly greater proportion of the variance ( $F_{(4,73)} = 1.63$ ,  $p > .05$ ).

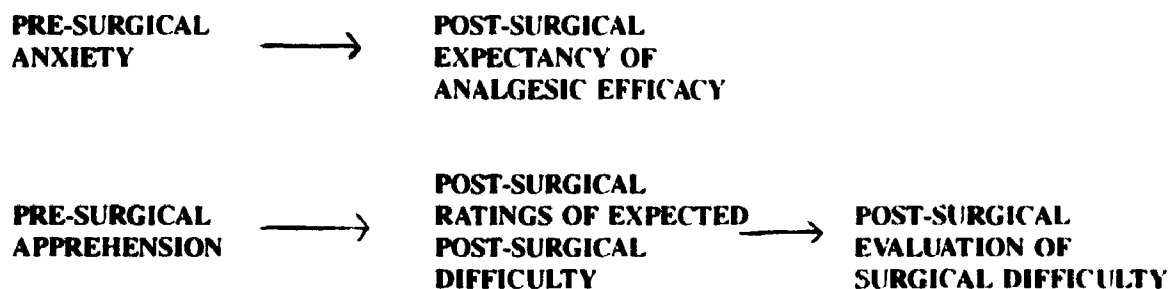
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<sup>11</sup> Only APPREHENSION and ANXIETY were entered because the ANALGESIC EFFECTIVENESS EXPERIENCED was collected only in the experimental subjects.

The second regression dealt with EXPECTED POST-SURGICAL DIFFICULTY. After the 1st step, APPREHENSION was entered,  $R^2 = .41$ ,  $F = 55.39$ ,  $p < .000$ . After the second step, DIFFICULTY was added to the prediction of EXPECTED POST-SURGICAL DIFFICULTY by APPREHENSION,  $R^2 = .46$ ,  $F = 32.95$ ,  $p < .000$ . No other variables were entered in the equation. Entering all the variables in another regression equation yielded an  $R^2 = .47$  which did not account for a significantly greater proportion of the variance ( $F_{(3,72)} = .41$ ,  $p > .05$ ).

The third forward entry regression dealt with pill expectation (EXPECTANCY). Only ANXIETY was entered,  $R^2 = .10$ ,  $F = 8.64$ ,  $p < .04$  in the regression equation. Entering all variables in another regression equation yielded an  $R^2 = .15$  which did not account for a significantly greater proportion of the variance ( $F_{(4,73)} = .93$ ,  $p > .05$ ) than ANXIETY alone.

*In summary, the results of the regression data of this study suggests that anxiety level prior to surgery is the best predictor of expectancy for analgesic efficacy, while APPREHENSION level predicted EXPECTED POST-SURGICAL DIFFICULTY which in turn predicted difficulty. The pattern of relationships suggested by the regression approach is presented in Figure 12. These results must be interpreted with caution not only because of the small number of subjects per cell, but also because the data was not collected in a fashion which inferences about causal relationships can be made.*

**Figure 12 - Relationship among Surgical Factors****Post-Surgery Period**

**Post-Surgery Take Home Measures.** After surgery, all subjects were given a vial containing 12 doses of medication to take home. Each dose of the medication contained the equivalent of the pharmacologically active ingredients found in Tylenol<sup>®</sup>3. However, lo-expectancy control subjects and experimental subjects were given 12 white capsules described as "analgesic enhancers". On the other hand, hi-expectancy control subjects and experimental subjects were given 12 white capsules and 12 red and white capsules described as "analgesic enhancers" and "analgesics typically used in oral surgery", respectively. An additional group of 15 subjects received 12 McNeil Consumer Product Tylenol<sup>®</sup>3 without any alterations of expectation.

All subjects (regardless of group assignment) were instructed to take the first dose of post-surgical medication "just when the effects of the local anaesthetic start to wear-off and just before beginning to experience post-surgical pain".

Ingesting three doses of the medications at 3- to 4-hour intervals constituted the requirement for participation in the study. Immediately after taking each dose, subjects were instructed to: 1) complete the McGill Pain Questionnaire and; 2) rate on VASs

the pain intensity and the unpleasantness of the post-surgical sensations. After taking the analgesic, subjects were to rate the post-surgical sensations four additional times (assessment periods) at 1/2 hour, 1 hour, 2 hours, 3 hours.

***Initial/Unpleasantness Levels.*** In order to ensure that subjects in all seven groups followed the instructions in the same manner and started to take the medication when they experienced similar levels of pain/unpleasantness, the McGill Pain Questionnaire Scores (sensory, affect, evaluative, miscellaneous, total scores) and the VAS-intensity and unpleasantness scores immediately after taking the first dose of analgesic were subjected to One-Way Analyses of Variance as a test for main effect for group. Whenever the assumption of homogeneity of Variance was violated, non-parametric Kruskal-Wallis analyses of variance were used analogously to the F-test.

The sampling distributions for the McGill Pain Questionnaire subscores did not meet the assumption of homogeneity of variance. Results of the non-parametric tests indicate that upon taking the first dose of post-surgical analgesic, there were no significant group differences in any of the subscales or in the total pain intensity score ( $\chi^2_{(99)} = .57$ ;  $p = .47$ ). Similarly, F-ratios for VAS-intensity and VAS-unpleasantness measures did not yield an overall main effect for groups ( $F_{\text{intensity } (6,95)} = .80$ ;  $p = .57$ ;  $F_{\text{unpleasantness } (6,95)} = 1.36$ ;  $p = .24$ ).

Thus, it is concluded that all groups followed instructions in the same manner because they did not differ in the level of sensory intensity nor unpleasantness ratings when they took the first dose of post-surgical analgesic.

***Post-Surgical Analgesic Efficacy.*** The visual analogue scale measures of pain intensity and unpleasantness were combined to produce various measures of analgesic



efficacy. The method used to combine these measures is similar to that suggested by Cooper and Beaver (1977).

**PID and PUD -**

Pain intensity and pain unpleasantness difference scores were derived by subtracting VAS ratings immediately after taking a dose of analgesic from VAS ratings at each assessment period. Thus, yielding four **PID** scores and four **PUD** scores for each of the 3 doses of analgesic taken by each subject.

**SPID and SPUD -**

Sum of pain intensity and unpleasantness difference scores - a measure of the area under the time-effect curve derived by summing **PID** scores and **PUD** scores over the four rating periods. Thus, yielding one **SPID** score and one **SPUD** score for each of the 3 doses of analgesic taken by each subject.

**PEAK PID and PEAK PUD -**

Were derived by taking the greatest effect reported by each subject within the four assessment periods. Thus, yielding one **PEAK PID** and one **PEAK PUD** score for each of the three doses of analgesic taken by each subject.

The following measures were also computed:

- 1) The proportion of subjects in each group who reported at least 40% pain/unpleasantness reduction for at least one of the four assessment periods (**PROPORTION WITH 40% PAIN/UNPLEASANTNESS REDUCTION**);
- 2) The total number of rating periods for which at least a 40% pain/unpleasantness reduction was obtained (**NUMBER OF PERIODS WITH 40% PAIN/UNPLEASANTNESS REDUCTION**).

Total scores for these measures of analgesia (**SPID, SPUD, PEAK PID, PEAK PUD, PROPORTION WITH 40% PAIN/UNPLEASANTNESS REDUCTION, PERIODS WITH 40% PAIN/UNPLEASANTNESS REDUCTION**) were summed

over the three doses of analgesic to yield overall total scores for each subject on each measure.

**Hypothesis 4.** It was expected that expectancy manipulations would influence the level of post-surgical analgesia and unpleasantness relief reported by subjects. Specifically, hi-expectancy subjects were expected to report greater levels of analgesia and unpleasantness relief than lo-expectancy subjects. Moreover, subjects who received hi-expectancy instructions were expected to report significantly greater post-surgical relief than subjects in the Tylenol #3 group. The SPID, SPUD, PEAK PID AND PEAK PUD scores were analyzed using One-Way Analyses of Variance F test as the overall test for differences among groups. These were followed by a series of six contrasts: 1) lo-expectancy control vs. lo-expectancy experimental groups; 2) hi-expectancy control vs. hi-expectancy experimental; 3) experimental groups who received an analgesic (hi-expectancy/analgesic; lo-expectancy/analgesic) vs. those who received a placebo (lo-expectancy/placebo; hi-expectancy/placebo); 4) lo-expectancy control vs. hi-expectancy control; 5) lo-expectancy control vs. Tylenol #3; 6) hi-expectancy control vs. Tylenol #3. The results of the OneWay Analyses of Variance performed on the various measures of post-surgical analgesia and unpleasantness relief revealed: 1) no significant main effects for groups on any rating of unpleasantness; 2) a significant main effect for group on most of the measures of pain reduction. An analysis of contrasts revealed that: 1) hi-expectancy control subjects reported significantly greater post-surgical pain reduction than lo-expectancy subjects; 2) lo-expectancy control subjects reported significantly less post-surgical pain reduction than either the lo-expectancy experimental subjects or the Tylenol #3 control subjects.

Table 12 presents the results of the analyses of variance on SPID and PEAK SPID.

Figures 13 and 14 depict the SPID and PEAK SPID scores at each of the three doses for each group and provide a visual corroboration that: 1) in general, hi-expectancy subjects experienced more post-surgical analgesia than lo-expectancy subjects; 2) the Tylenol #3 unaltered expectancy control group experienced the greatest levels of post-surgical analgesia.

Additional analyses on the **PROPORTION WITH 40%**

**PAIN/UNPLEASANTNESS REDUCTION and PERIODS WITH 40%**

**PAIN/UNPLEASANTNESS REDUCTION** also served to corroborate the finding that hi-expectancy of analgesic efficacy resulted in greater levels of post-surgical analgesia for hi-expectancy groups. Chi Square tests of 1) proportion of subjects who reported at least 40% pain relief at any hour and, 2) proportion of rating periods with at least 40% pain relief were significant ( $\chi^2_{(4)}=15.37$ ,  $p<.005$ ;  $\chi^2_{(4)}=24.78$ ,  $p<.001$ , respectively) and these results are apparently due to a greater proportion of hi-expectancy subjects reporting at least 40% pain relief at any hour and having a greater proportion of rating periods in which they reported at least 40% pain relief (Table 13). Chi Square tests of proportion of subjects who reported at least 40% unpleasantness relief was significant ( $\chi^2_{(4)}=11.11$ ,  $p<.025$ ) and this result is apparently due to a greater proportion of hi-expectancy subjects reporting at least 40% unpleasantness relief at any hour. The Chi Square test of proportion of rating periods with at least 40% unpleasantness relief was not significant.

**Table 12 F-Ratios and Contrasts Analyses for Post-Surgical Pain Data over 3 Doses**

VARIABLE	F-Ratio	CONTRASTS (t values)							
		Lo-Expectancy Control vs Lo-Expectancy Experimental	Hi-Expectancy Control vs Hi-Expectancy Experimental	Analgesic vs Placebo	Hi-Expectancy vs Lo-Expectancy Control	Lo-Expectancy Control vs Tylenol 3	Hi-Expectancy Control vs Tylenol 3		
SPID	2.47*	2.25	1.21	-1.28	2.39*	3.48****	1.31		
PEAK SPID	2.59*	2.94**	0.39	-1.12	2.57*	3.19***	1.33		

\* p < 0.02  
 \*\* p < 0.01  
 \*\*\* p < 0.005  
 \*\*\*\* p < 0.001

Figure 13 Group Means for the Sum of Pain Intensity Difference Scores (SPID) over the Three Doses of Analgesic.

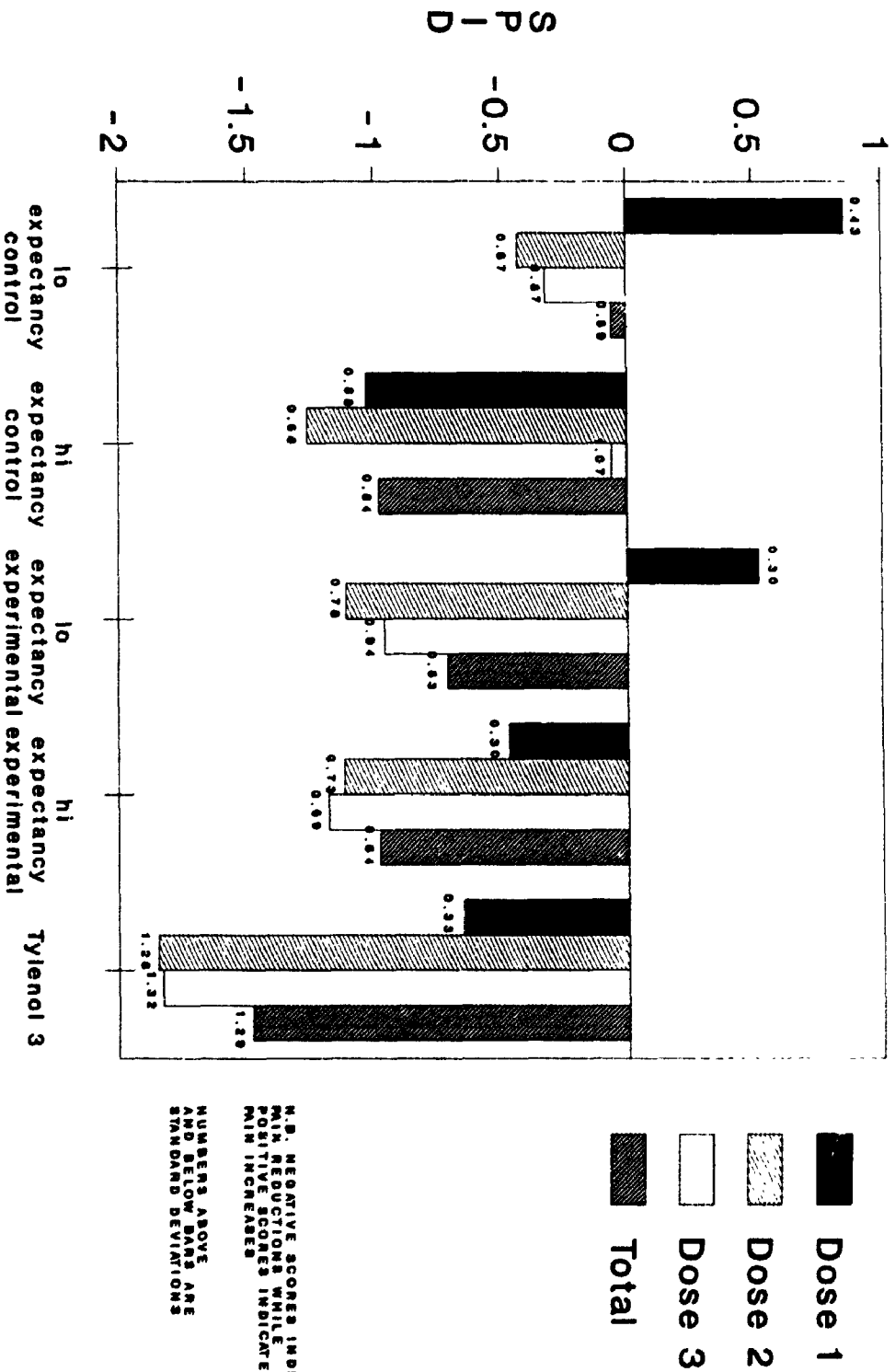


Figure 14 Group Means for the Peak Pain Intensity Difference Scores (PEAK PID) over the Three Doses of Analgesic

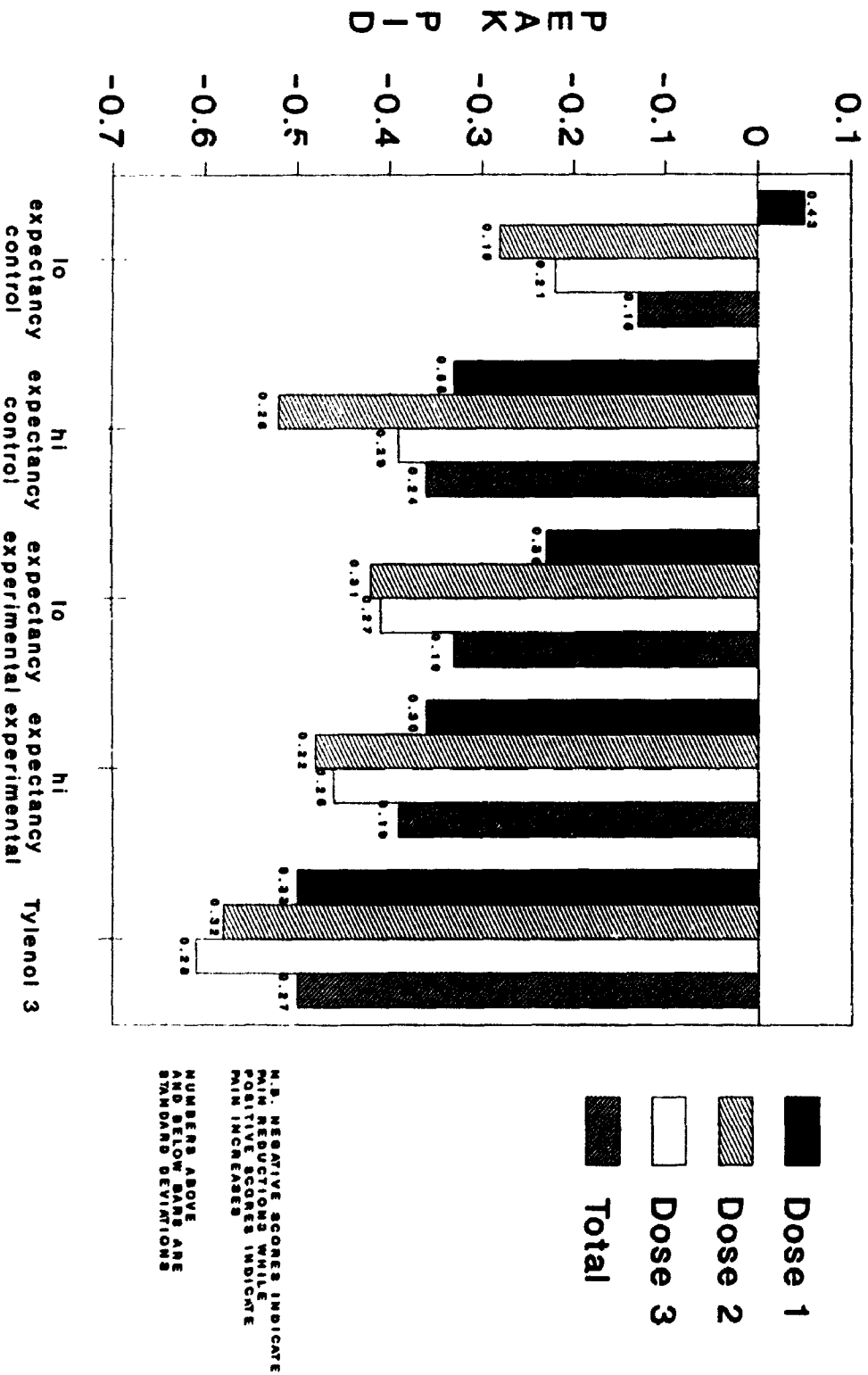


Table 13 Proportion of Subjects and Rating Periods with at least 40% Pain/Unpleasantness Relief

Group	PID		PUD	
	Proportion of Subjects with at Least 40% Pain Relief in Any Period	Proportion of Rating Periods with at Least 40% Pain Relief	Proportion of Subjects with at Least 40% Unpleasantness Relief in any Period	Proportion of Rating Periods with at Least 40% Unpleasantness Relief
Lo-Expectancy Control	0	0	9%	45%
Hi-Expectancy Control	50%	26%	30%	50%
Lo-Expectancy Experimental	35%	16%	26%	52%
Hi-Expectancy Experimental	50%	25%	45%	70%
Tylenol®3	50%	44%	50%	60%

$$\chi^2_{(4)} = 15.37^{**}$$

$$\chi^2_{(4)} = 24.78^{**}$$

$$\chi^2_{(4)} = 11.11^{**}$$

$$\chi^2_{(4)} = 6.98$$

\*\*\*  $p < .001$ \*\*  $p < .005$ \*  $p < 0.25$

*In summary, although all subjects received the same pharmacologically active ingredients after surgery, there were significant group differences in the levels of post-surgical analgesia reported by subjects. As predicted, expectancy instructions have significantly influenced the levels of post-surgical analgesia reported by subjects. In general, the lo-expectancy control subjects reported significantly less post-surgical analgesia than the hi-expectancy controls or the Tylenol<sup>®</sup>3 controls. On the other hand, differences in the levels of analgesia reported by hi- and lo-expectancy experimental subjects did not reach statistical significance, thus suggesting that prior experience with the instructions and the pharmacological (or placebo) effects of the drug tend to reduce the effects of expectancy manipulations. The unaltered expectation group that received McNeil Pharmaceutical Tylenol<sup>®</sup>3 brand pills reported the greatest levels of post-surgical analgesia. This is not surprising since expectancy for this drug is very high. In fact, 18% of the subjects in this experiment rated Tylenol<sup>®</sup>3 as the most effective analgesic; 34% rated it as the second most effective analgesic. Only 32 patients did not mention Tylenol<sup>®</sup>3 as one of the 2 most potent analgesic drugs. Of these, however, 53% of the subjects rated codeine (a commonly known analgesic found in Tylenol<sup>®</sup>3) as one of the 2 most effective analgesics available.*

*Anecdotal evidence also supports these findings. Six of the lo-expectancy subjects contacted the experimenter the evening of their surgery because they were concerned about the inefficacy of the analgesic, whereas only one of the hi-expectancy subjects and none of the Tylenol<sup>®</sup>3 subjects contacted the experimenter. Of the pool of subjects, 14 deliberately switched to an analgesic which was perceived to be more effective than the experimental analgesic. Six of the fourteen switched to name brand Tylenol<sup>®</sup>3; one*



*switched to Tylenol <sup>#</sup>1; three switched to extra strength Tylenol; one switched to 292's; two to 222's and one person switched to Advil. All fourteen rated the alternate analgesic as much more effective than the experimental analgesic.*

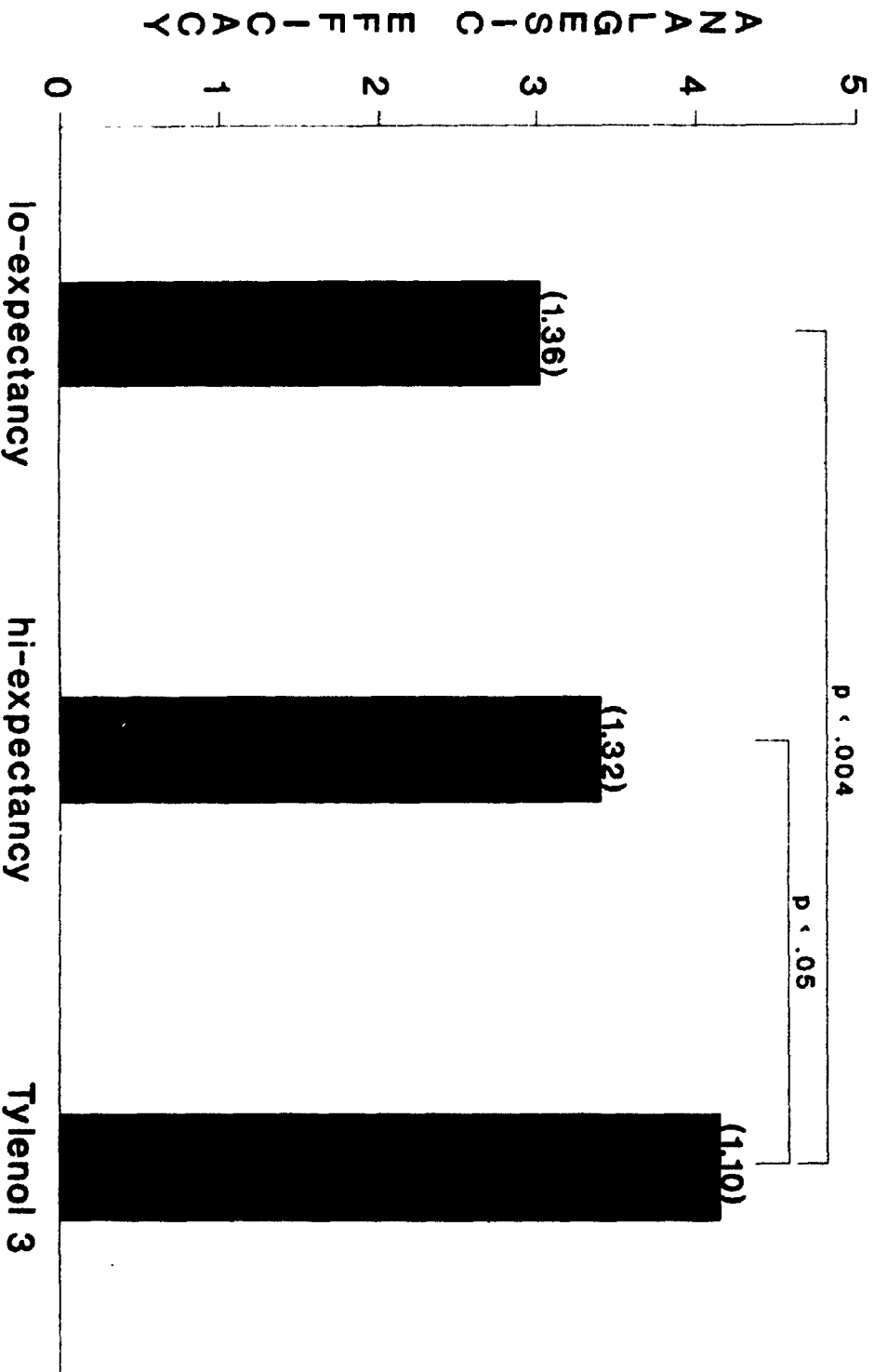
### **Post-Surgical Qualitative Data**

Over the course of recovery from surgery, additional measures were collected to enhance the understanding of the relationship among expectancy, analgesic efficacy and recovery from surgery. The measures collected were: 1) overall rating of analgesic efficacy (on a 5-point rating scale ranging from "got rid of no pain at all" to "got rid of all the pain"); 2) VAS rating of post-surgical pain experienced compared to expected; 3) number of hours to eat for the first time; 4) number of hours to eat normally; 5) number of hours to return to work; 6) number of experimental analgesics taken; and 7) number of other analgesics taken specifically for post-surgical pain. Each of these additional measures were analyzed separately.

**Ratings of Analgesic Efficacy.** Congruent with differences in post-surgical ratings of pain obtained, a significant group main effect was obtained for rating of analgesic efficacy ( $F_{(6,88)}=4.25$ ;  $p<.02$ ). Figure 15 presents the mean analgesic effectiveness for each level of expectancy. Post-hoc contrasts revealed significant differences between: 1) lo-expectancy groups and Tylenol <sup>#</sup>3 ( $t=-3.19$ ;  $p<.004$ ) and; 2) hi-expectancy groups and Tylenol <sup>#</sup>3 ( $t=-2.07$ ;  $p<.05$ ). No significant differences were obtained between hi-expectancy and lo-expectancy groups.

**Post-surgical pain experienced compared to expected.** An analysis of variance of subjects' ratings of level of pain experienced compared to level of pain expected did not yield a significant group main effect.

Figure 15 Mean Ratings of Analgesic Efficacy by Level of Expectancy

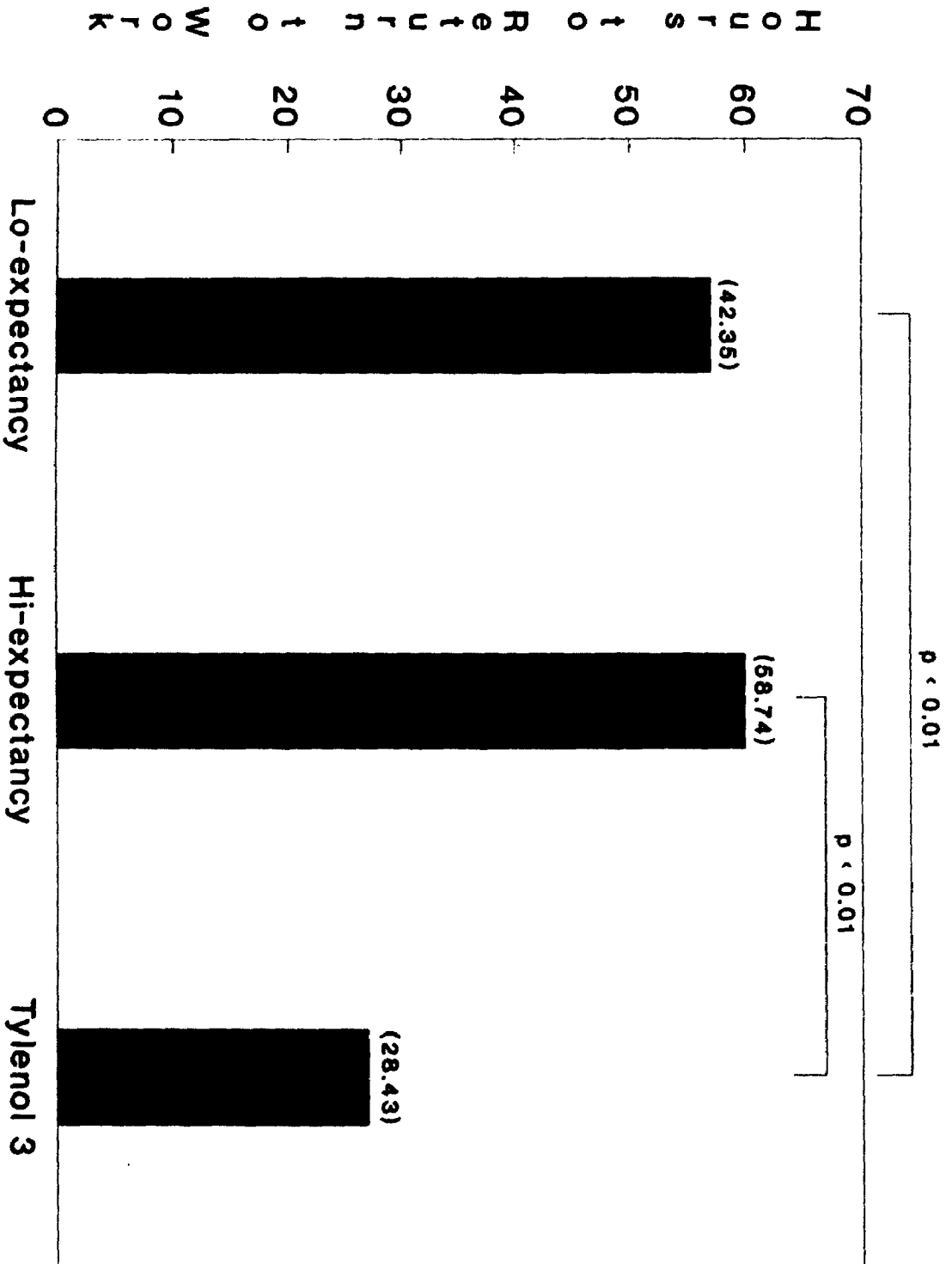


N.B. Numbers above bars are standard deviations.

**Hours to eat; Hours to eat normally; Hours to return to work.** The three measures were subjected to one way analyses of variance. No significant group differences were obtained for hours taken to eat nor for hours taken to eat normally. A significant main effect for hours to return to work was obtained. Post-hoc contrasts indicated that the lo-expectancy groups took significantly longer to return to work than the Tylenol<sup>®</sup>3 group ( $t=2.64$ ;  $p<.01$ ). Figure 16 depicts hours to return to work as a function of expectancy.

**Number of experimental analgesics taken.** The distribution of scores for these measures did not meet the assumption of homogeneity of variance. The proportion of subjects who took <5, 5-11 and all 12 pills was computed for each level of expectancy. Table 14 presents a significant difference in the proportion of subjects who took fewer than 5 pills ( $\chi^2=11.25$ ;  $p<.01$ ) and this result apparently is due to a greater proportion of subjects in the hi-expectancy groups (hi-expectancy and Tylenol<sup>®</sup>3) who took fewer than 5 pills. The Chi-Square test for the proportion of subjects per group who took all 12 pills was significant ( $\chi^2=16.16$ ;  $p<.001$ ) and this result is apparently due to the greater proportion of lo-expectancy subjects who took all 12 of the prescribed analgesics.

Figure 16 Hours Taken to Return to Work



N.B. Numbers above bars are standard deviations.

<b>Table 14      Proportion of Subjects Who Took X Number of the Experimental Analgesic as a Function of Expectancy</b>			
	Took < 5	5 < Took < 11	Took all 12
Lo-Expectancy	33%	34%	33%
Hi-Expectancy	53%	32%	15%
Tylenol 3	86%	14%	0%

$$\chi^2=11.25, p<0.01 \quad \chi^2=4.5, p<0.15 \quad \chi^2=16.16, p<0.001$$

**Number of other Analgesics Taken.** The distribution of scores for this measure did not meet the assumption of homogeneity of variance. Table 15 presents the proportion of subjects who took and who did not take other analgesics as a function of level of expectancy. The Chi-Square on this proportion ( $\chi^2=7.94, p<.02$ ;  $\chi^2=4.11, p<.15$ , respectively) indicate that when compared to hi-expectancy subjects and Tylenol <sup>R</sup>3 subjects, a significantly greater proportion of lo-expectancy subjects took other analgesics in addition to the experimental analgesics.

<b>Table 15      Proportion of Subjects Who Took and Who Did not Take Other Analgesics as a Function of Expectancy</b>		
	Did not Take Other Analgesics	Took Other Analgesics
Lo-Expectancy	48%	52%
Hi-Expectancy	81%	18%
Tylenol 3	71%	28%

$$\chi^2=4.11, p<0.15$$

$$\chi^2=7.94, p<0.02$$

*In summary, although all subjects received the same pharmacologically active ingredients after surgery, expectancy manipulations in this experiment seem to have influenced subjects' perception of the analgesic's effectiveness (Figure 13). Both lo- and hi-expectancy subjects reported significantly less analgesic efficacy than the Tylenol <sup>®</sup>3 group. In addition to perceived efficacy of the analgesic, the expectancy manipulations have also influenced: a) how quickly patients returned to work; b) how many of the experimental analgesic pills they took; c) whether they took other non-prescribed analgesics. Thus, the level of expectancy communicated to patients not only influenced how much post-surgical pain they experienced, but it also influenced how quickly they returned to work and how many analgesics they took.*

## **CHAPTER SIX**

### **Discussion**

The current study manipulated expectation of analgesic efficacy in an experimental context in an effort to isolate the independent effects of expectancy from the pure pharmacological effect of the analgesic. For the experimental phase of the study, subjects were divided into two groups, a hi-expectancy group who were made to expect a potent drug and a lo-expectancy group who were made to expect an ineffective drug. In either case, half of each group actually received a potent analgesic while the other half received a placebo. Several researchers in this field have suggested that the balanced placebo design is the only methodology which allows for the parcelling out of the independent effects of expectancy from the drug effects (Marlatt and Rohsenow, 1981). Although common in alcohol studies, this design had not been previously applied to the study of analgesic efficacy.

The effect of expectation of analgesic efficacy was then evaluated in a clinical pain context. Again, some subjects were told that they would receive an ineffective drug and other subjects that they would receive a potent analgesic when in fact, all subjects were given the pharmacological equivalent of Tylenol #3.

The final intent of the study was to demonstrate that expectations of analgesic efficacy not only play a role on how much pain is reported after surgery but also influences other post-surgical recovery indices such as how many analgesics are taken and how long it takes both to resume normal eating and to return to work. The following discussion focuses on the theoretical and clinical implications of the results and examines them in light of the existing models which have been proposed to explain

expectancy effects. In addition, the methodological limitations of the study and future directions for research are addressed.

### **The Effects of Expectancy on Experimental Pain**

As predicted, the two sets of expectancy instructions produced significantly different levels of expectation. This difference in expectancy between the hi- and the lo-expectancy groups, persisted even after subjects had first-hand experience with the effects of the drug or the placebo. Thus, the study demonstrated that two different sets of expectation of treatment effectiveness can be established in a fairly straightforward manner in an experimental pain context.

**Pain intensity/unpleasantness.** As expected, when compared to the lo-expectancy subjects, the hi-expectancy subjects reported reduced levels of pain intensity 45 minutes after ingesting the pills(s). They did not, however, show statistically significant reduced levels of subjective ratings of unpleasantness. According to Turk, Meichenbaum & Genest (1983), the meaning of the pain greatly influences a subject's perception of a painful stimulation. Thus, the absence of a significant difference in unpleasantness is not surprising given that experimental pain does not evince a strong emotional component since the meaning of pain to the individual tends to be neutral to positive ("I am doing a good deed and helping this poor woman get her Ph.D."). Additionally, the sense of impending harm to tissue or to health was greatly reduced because subjects were given assurances that the stimuli was of short duration, safe and would not produce tissue damage.

Neurophysiological evidence discussed by Melzack (1990) also suggests that the sensory dimension of the experimental pain experience might be psychologically more



salient than the affective dimension. Thermal nociceptive stimulation produces a quick acting pain (phasic pain) believed to be transmitted from the dorsal horn to supraspinal structures via the lateral tract-- shown to be mostly responsible for discrimination of location and type of pain perception. Tonic pain (e.g. long lasting pain following surgery), on the other hand, is believed to be transmitted by the medial tract-- shown to be mostly responsible for the motivational affective dimensions of pain perception because it goes to the brain via the limbic system.

Because a number of extant studies in the alcohol literature have demonstrated that expectancies had a greater effect on subjects' psychological and physiological responses than did the presence of alcohol (e.g., Abrams & Wilson, 1979; Hull & Bond, 1986), it was expected that high expectancy subjects would experience analgesia whether they received a drug or a placebo. While the results supported this hypothesis, a surprising finding is that there were no significant differences in pain and unpleasantness ratings between the drug and placebo conditions. In other words, while it indeed mattered what a subject's expectations had been about the treatment he/she would receive, it did not matter whether the actual treatment had been an analgesic or an inert substance when he/she reported pain and unpleasantness sensations.

Therefore, the experimental effect that can be attributable mainly to psychological mechanisms was more powerful than that attributable to pharmacological action. Five explanations could be postulated for the finding.

- 1) It could be argued that the lack of drug effects was due to subjects' responding to demand characteristics. That is, subjects responding in a way which matches their perception of study objectives. In other words, lo-expectancy subjects who

received an analgesic may have purposefully biased their responses to pain to suggest little analgesia while hi-expectancy subjects who received a placebo may have purposefully exaggerated their responses to pain to suggest a lot of analgesia. Given the careful methodological precautions taken to reduce demand characteristics within this study, this explanation is unlikely for the following reasons:

- a) in the pilot study, all subjects felt free to report relief should they experience it. Thus, providing a test to demonstrate that the instructions did not explicitly produce response biases in subjects who received either hi- or lo-expectancy instructions.
- b) the subjects in each group were absolutely unaware of the presence of other experimental groups not receiving the same treatment<sup>12</sup> — thus, reducing the chances that they could form hypotheses about the objectives of the study.
- c) subjective responses were obtained four times for each of the four stimulus temperatures making it quite difficult for subjects to bias their responses deliberately so that their responses could correspond to their perceptions of experimental demands. Again, even if this had been possible, subjects received very few cues as to what the experimental demands were.

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<sup>12</sup>The letter of explanation did not suggest in any way that drugs were being compared or that other experimental conditions existed.

- d) the reduction (although not significant) in the subjective levels of sensory intensity reported by the lo-expectancy analgesic subjects indicates that subjects who unknowingly received the analgesic felt comfortable in reporting lower levels of sensory intensity even though this effect was not suggested directly in the experimental instructions.
- 2) The robustness of the analgesic effects of Tylenol <sup>®</sup>3 was perhaps reduced significantly given that in the experimental condition, expectancy level was the only cue against which subjects could judge their experience. It is worthwhile to note, however, that although not statistically significant, subjects in the lo-expectancy/analgesic group did report some reduction in their perception of the sensory intensity 45 minutes after receiving the pill. This suggests that Tylenol <sup>®</sup>3 produced some analgesic effects, albeit not as strong as the effects produced by expectancy. In this study, ethical and procedural constraints<sup>13</sup> prevented the use of a stronger dose of analgesic (i.e. 2 tablets of Tylenol <sup>®</sup>3 instead of 1). Extant studies which examined the analgesic effectiveness of Tylenol <sup>®</sup>3 used a double dose. It could be argued that in this study, the relatively greater effect of expectancy was due to the fact that subjects were not given a high enough dose of Tylenol <sup>®</sup>3. Had lo-expectancy/analgesic subjects received 2 doses of Tylenol <sup>®</sup>3, they too may have exhibited significant reductions in pain ratings.

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<sup>13</sup> The author was given authorization to carry out the study in oral surgery provided that she did not require a change in the usual procedure which is observed in the oral surgery department (re: dosage of Tylenol <sup>®</sup>3).

- 3) Because the pain does not have an important meaning for the individual, there may be less of a need to respond to the pharmacological effects of the analgesic. If this is true, one would expect the importance of expectancy to be reduced in a clinical pain setting where it is important for the individual to obtain pain relief regardless of what is communicated verbally. The results of the clinical pain portion of this study show that the analgesic efficacy of Tylenol<sup>®</sup>3 for reducing post-surgical pain depends largely on expectancy. Thus, this explanation is not tenable.
- 4) Based on past studies, it was assumed that the pain measurement method of magnitude estimation (visual analogue scale) was an absolute scale implying that the direct judgements of sensory intensity not only reflect the relative position of the stimuli being judged, but also allow for the assessment of level differences in sensation. The magnitude estimation method used in this study to evaluate subjective ratings of pain and unpleasantness may not have been sensitive enough to assess level differences in sensation for such a small number of individuals in each group (i.e. N=15/group). A recent paper which compared the reliability and sensitivity of category rating scales and magnitude estimate scales for judging pain pressure stimuli (Ellermeier & Westphal, 1991) provides evidence to support the assertion that in this study, the magnitude estimate scales may not have been sensitive enough to detect group differences — especially because of the relatively small number of subjects per group. They demonstrated that when two different sets of subjects judge different stimulus ranges, both magnitude estimation and category rating scales resulted

in an accurate reflection of the relative positions of the stimuli being judged. However, only category scales were sensitive enough to differentiate between the two stimulus ranges.

- 5) Finally, it could be argued that within an experimental pain context, expectancies are more important than the presence or absence of an active drug in determining subjective reports of pain reduction -- a conclusion which is strongly supported by extant studies in the alcohol literature.

The cognitive mechanism by which this occurs may well be due to selective monitoring of positive cues which predicts that subjects who received instructions for increased expectancy of analgesic efficacy may have: 1) selectively paid attention to internal and external cues which were congruent with analgesic effects (Skelton and Pennebaker, 1982), or 2) may have emphasized small positive changes (Lick and Bootzin, 1975), or 3) may even have chosen to interpret ambiguous somatic sensations according to their expectancies and thus label them as positive changes (Dinnerstein and Halm, 1970). The following evidence lends support to this explanation: a) subjects in the hi-expectancy groups reported significantly more side-effects; and b) a greater proportion of subjects in the hi-expectancy group reported side-effects. Although it can safely be concluded that in this context expectancies were a more robust determinant of analgesic efficacy than was the presence or absence of an active drug, the active drug may have had a significant effect which was not detected due to the lack of sensitivity in the magnitude estimation scale used to measure sensory intensity.

Recent advances in the area of neurophysiological processing of somatosensory stimuli can also help to shed light on our understanding of the result that expectancy seemed to be more important in predicting levels of analgesia than was the presence or absence of an analgesic. A brief review of spinal cord pain mechanism is required to develop an understanding of the application of neurophysiological processing to the results of the current study. Information about pain is delivered to the dorsal horns of the spinal cord by peripheral neurons emanating from the skin (and other body tissues). Ascending neurons originating in the dorsal horns then relay the pain signals upward through the spinal cord to the various parts of the brain. Recent advances in neuropsychophysiology have led to the realization that there is not a direct relationship between somatosensory stimulation and ultimate pain perception (Melzack and Wall, 1965, 1989). Instead, the relationship between nociceptive stimulation and pain perception depends on several modulatory processes in the dorsal horn and in the brain. Studies with primates (Hayes, Dubner & Hoffman, 1981; Hayes, Price & Dubner, 1979; Hoffman, Dubner, Hayes & Medlin, 1981) have shown that responses of neurons in the dorsal horn (both wide dynamic range (WDR) and nociceptive specific (NS)<sup>14</sup>) could be modulated by different attentional sets and different conditions of stimulus relevance (Price, 1988). They have shown that the area of the receptive fields of WDR and NS neurons could expand or contract as a function of the attentional set of the animal. When the experimental condition demanded that the

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<sup>14</sup>WDR- somatosensory neurons located in the dorsal horn. These neurons have larger receptive fields than most primary afferent neurons. Stimulation of these neurons produces pain. These neurons respond maximally to nociceptive stimuli.

NS- somatosensory neurons that respond exclusively to nociceptive stimuli. They are found in high concentration in the dorsal horns.

animal pay attention to thermal stimuli, the area of the receptive fields of WDR and NS neurons expanded in response to noxious thermal stimuli. Conversely, when the experimental condition demanded that the animal pay attention to visual cues, the area of the receptive fields of the WDR and NS neurons contracted in response to noxious thermal stimuli. This result indicates that attentional sets that are stimulus-relevant would have the effect of recruiting a greater number of dorsal horn sensory projection neurons. An effect which would in turn result in increased perceived intensity of the nociceptive thermal stimuli. Thus, the composition of centrally-activated neurons (in this case largely determined by attentional cues) can have as direct a role in determining somatosensory perception as the peripheral stimuli themselves.

If this line of evidence is applied to the results of the present study, it could be argued that hi- and lo-expectancy subjects may have been under different attentional sets. Specifically, the instructions to the lo-expectancy subjects alerted the subjects that we were interested in the type of effects produced by the capsule--"we want to see what the effects of the capsule are alone" (i.e. without the analgesic). For the hi-expectancy subjects, on the other hand, there were no doubts that we were looking for analgesic effects of the capsules. This difference in the instructions given to lo-expectancy subjects could very well have heightened the attention subjects gave to the thermal stimuli and in so doing, mask some of the pharmacological analgesic effects in the lo-expectancy/analgesic group. Given what we know about the relationship between somatosensory perception and attentional sets, the instructions to the lo-expectancy subjects might result in the recruitment of a greater number of dorsal horn sensory projection neurons which would in turn result in increased perceived intensity

of the nociceptive thermal stimuli. It would be expected that this effect would produce increased pain perception for the lo-expectancy/placebo subjects and a 'dulling' of the analgesic effects of Tylenol <sup>®</sup>3 for the lo-expectancy/analgesic subjects. Examination of the results (Figure 6, pg.72) provides partial support for this explanation.

Neurophysiological evidence to support the fact that in humans, cognitive factors, such as attentional set, can not only have as direct a role in determining somatosensory perception of the peripheral stimuli themselves, but that they could also serve to dull the effects of a potent analgesic would challenge the prevailing view of the treatment of pain. Certainly, such a demonstration would help clinicians and researchers in this field understand better the role of situational and contextual factors not only important in modulating pain perception, but also critical in determining the effects of analgesics.

**Linear Transformation of Experimental Data and Suggested Mechanism of Action.** As discussed by Price (1988), visual analogue scale responses to contact-heat-induced pain stimuli have been repeatedly shown to follow a power function relationship whose exponent is equal to the slope of the corresponding linear function. According to previous studies in this area, central inhibitory analgesia produces reductions of different intensities of pain sensations by a nearly constant numerical extent — that is, responses to low intensity stimuli will be reduced to a relatively greater extent than responses to higher intensity stimuli. Thus, one would expect that analgesia which is mediated through central inhibitory mechanism would produce a log transformed function which has both a different y-intercept and a different slope (since post-analgesic pain ratings of lower intensity stimuli will be reduced to a relatively



greater extent than higher intensity stimuli). Examination of the linear transformed data in this study (Figure 8 and Figure 9; p. 81, 83) provides evidence to postulate a central-inhibitory mechanism of action for the two groups who received codeine and acetaminophen. This result is not surprising given that codeine (given to subjects in the lo-expectancy/analgesic and the hi-expectancy/analgesic groups) would be expected to produce analgesia through a central-inhibitory analgesic mechanism. The data for the two groups who did not receive an active drug also follows a pattern similar to that obtained for central inhibitory analgesic. Unfortunately, the relatively small number of subjects in each group prevents from reaching a firm conclusion about the mechanism of action.

**Expectancy Levels and Anxiety.** When compared to their lo-expectancy counterparts, it was anticipated that hi-expectancy subjects would experience less anxiety because they were told they would receive a potent analgesic plus an enhancer. In fact, hi-expectancy subjects experienced significantly higher levels of anxiety immediately after receiving the drug. This effect was evident even after the effects of trait anxiety were partialled out. Hi-expectancy instructions could have increased anxiety by: 1) increasing subjects' concerns about the possible physiological effects of this potent combination of analgesic and analgesic enhancer; and/or 2) increasing the perception of experimental demands of subjects to perform and to demonstrate some change in subjective evaluation of pain.

After having experienced the effects of the analgesic (or the placebo), subjects rated their anxiety again. Interestingly, hi-expectancy subjects who received an analgesic are the only ones who showed a significant reduction in anxiety. The hi-

expectancy/placebo subjects reported a small but non-significant reduction while the lo-expectancy subjects (both analgesic and placebo) experienced a small increase. The observed increase on the part of lo-expectancy subjects after experiencing the effect of the drug (or placebo) is consistent with the fact that subjects were told that they would receive the same drug after surgery as they had received in the experimental session.

It has been proposed by Gracely, McGrath & Dubner (1979) that placebos could act primarily by reducing the unpleasantness dimension of the pain experience. This was not supported in the present study. Unpleasantness reductions reported in previous studies may have been due to the fact that placebos (or the drug-giving ritual) produced a reduction in anxiety and a subsequent change in the way sensory inputs were evaluated. Unfortunately, the current study does not allow for the postulation of a mechanism of interaction between anxiety levels and subsequent reductions in the unpleasantness dimension of the pain experience because the hi-expectancy placebo subjects rated themselves as significantly more anxious both in the study and as a trait. Therefore, the fact that these subjects did not report greater reductions in unpleasantness could also be explained by their heightened levels of anxiety.

**Expectancy Levels, Anxiety and Pain Perception.** The effect of anxiety on pain is still a controversial issue. Clinicians who specialize in pain control believe that anxiety intensifies pain (Chapman & Turner, 1986) while theorists in this area also postulate that increased anxiety influences psychological processes which result in increased pain perception (Melzack, 1973). On the other hand, others have suggested that anxiety decreases pain. There are animal studies (reviewed by Bolles and Fanselow, 1980) and human studies (Beecher, 1956, Bokey & Davidson, 1970,

Malow, 1981) to support the suggestion that anxiety has pain-reducing effects. Yet, others have suggested that anxiety influences pain through other factors such as attentional sets (Arntz, Dressen and Merckelbach, 1991).

In this study, the relationship between anxiety and pain was not easily interpretable. There was a trend (not statistically significant) for subjects who reported initial high levels of anxiety also to report smaller pain intensity reductions in the experimental session. Conversely, those who experienced low levels of anxiety tended to report greater levels of analgesia. The weakness of the relationship between anxiety and pain perception obtained in this study suggests that this relationship is probably mediated by a third factor such as the attention given to the painful stimulus (Beers & Karoly, 1979; Tan, 1982; Turk, Meichenbaum & Genest, 1983) or the meaning of the pain (Turk, Meichenbaum & Genest, 1983). Unfortunately, the results of this study do not permit an evaluation of the factors which may mediate the relationship between anxiety and pain perception. More research is needed to shed light on this relationship especially because it could have important clinical implications. For example, anxiety could have pain reducing effects in individuals for whom anxiety has the effect of increasing their level of interaction with environmental stimuli which would lead to reduced focus on pain stimuli and in turn alter pain perception. Conversely, anxiety could produce increases in pain perception in individuals for whom anxiety would have the effect of increasing the negative appraisal of incoming stimuli. Clearly, the relationship between anxiety and pain is mediated by a myriad of factors which need to be evaluated in well controlled studies.

### **Regression Model of Factors which Predict Analgesic Effects in an**

**Experimental Pain Context.** A regression approach was used to generate hypotheses for a mediator model in which various events (in this case in the experimental session) predict analgesic effects. This approach revealed that expectancy of analgesic efficacy, anxiety levels, and perception of pill's effects on physiological and subjective states (heart rate, blood pressure, anxiety) all predicted perceived levels of analgesic effects (as measured by the number of side effects reported and ratings of effect on pain perception). Levels of analgesic effects in turn predicted effects on subjective pain and intensity ratings of the stimuli. The model suggested by the results of this study is presented in Figure 10 (p. 93).

These results are somewhat surprising in that expectancy levels do not predict analgesic efficacy directly. Instead, the effects of expectancy are mediated through the subjects' assessment of the potency of the drug and subjects' perception of analgesic effectiveness. On the basis of existing literature, one would also have predicted that suggestibility would influence effectiveness by making subjects more or less credulous of the instructions provided in the study. Contrary to these assumptions, suggestibility was found to influence effectiveness directly without the mediating influences of the expectancy condition.

Caution must be exercised in making attributions of causality based on this regression model (Campbell & Stanley, 1963). Although the variables in the regression model were measured at different points in time, thus allowing for speculation about the direction of the relationship, statistically, attributions of causality are not possible within this regression model. The causal relationship among the factors identified in

the study could be tested more appropriately using a research design which would predict *a priori* the variables which form a factor. This model would need to be tested in a study specifically designed to describe causal relationships among variables. In such a study, the constructs (or factors) which have been identified could be measured with multiple indicators in order to increase the reliability of the variables (Baron & Kenny, 1986).

### **The Effect of Expectancy on Surgical Anxiety and Apprehension**

As predicted, subjects who experienced the greatest pain and unpleasantness relief during the experimental session were less anxious and less apprehensive about surgery. Thus, positive past experience with the effectiveness of an analgesic not only increased the expectancy of analgesic efficacy, but also reduced feelings of anxiety and apprehension about surgery.

Before surgery, the experimental subjects were significantly more anxious than the control subjects. This may be due to an attention difference (Arntz et al, 1991) between the two groups. When compared to control subjects, those who participated in the experimental phase of the study might have exercised more vigilance towards their feelings and concerns about surgery.

Of the experimental subjects, those who had received hi-expectancy instructions in the experimental session were significantly more anxious than those who had received lo-expectancy instructions. This finding conflicts with the intuitive prediction that individuals who have the most confidence in the analgesic effect of the drug would also experience less anxiety. The result is also surprising in light of the fact that intuitively, the subjects who experienced the highest levels of analgesia in the

experimental session should be those in the hi-expectancy groups. Thus, the relationship among past-experience with a drug, pre-surgical anxiety and expectancy of post-surgical analgesic efficacy is complex. The data collected in the present study do not clarify the relationship among those variables.

**Regression Model of the Relationship between Anxiety and Anticipated Surgical and Post-Surgical Difficulties.** The results of the regression analyses performed to generate hypotheses for a mediator model in which events in the pre-surgical session are used to predict post-surgical events suggests (Figure 12 depicts the relationship among the factors) no significant relationships between pre-surgical anxiety (statistically independent factor which consists of 3 different measures of anxiety) and expected post-surgical difficulty or ratings of surgical difficulty. Instead, it was the subjects' levels of apprehension about surgery (statistically independent factor which consists of subjects' pre-surgical evaluation of expected pain and unpleasantness both during and after surgery) which determined their post-surgical ratings of how much difficulty they would expect after surgery and how difficult they perceived the surgery to be. Thus, it seems that it is pre-surgical ratings of expected pain and unpleasantness during surgery, and not anxiety, that determines negative appraisal of surgery and expectation of difficulty after surgery. Methods aimed at reducing this apprehension should therefore result in less suffering for individual patients.

Thus, pre-surgical anxiety levels are not directly related to expectations of pain and negative appraisal of surgery. Instead, the present finding strongly indicates that strategies aimed at reducing apprehension seem to be more indicated than techniques or medicines for anxiety reduction.

Since fear of dentists and dental procedures is a prevalent problem in our society affecting a good portion of the population, and because this fear can be learned vicariously, every attempt should be used to reduce the trauma associated with dental procedures in order to minimize the development of apprehension in individuals and for the population at large. The results of this study indicate that the development of methods aimed at reducing patients' pre-surgical anticipation of pain during and after surgery is an avenue which could be taken to reduce patients' negative appraisal of the surgical procedure. The current practice of describing details to patients should therefore be supplemented with an accurate description of the sensations patients' might expect during surgery.

While caution must be exercised in interpreting the causal relationships tested by the regression model in the present study, important links between anxiety, apprehension, post-surgical evaluation of surgery and expected post surgical pain have been found and require further investigation in a study designed specifically to test causal relationships.

#### **The Effect of Expectancy on Post-Surgical Pain and Recovery from Surgery**

The experimental instructions successfully modified subjects' expectations of post-surgical analgesic efficacy. As anticipated, when compared to lo-expectancy controls, hi-expectancy controls had significantly higher expectations of analgesic efficacy for post-surgical pain. For experimental subjects, it appears that instead of rendering the expectancy instructions more salient, first-hand experience with the analgesic (or the placebo) had the effect of "dulling" expectancies -- the lo-expectancy experimental subjects had lower expectancies than the lo-expectancy control subjects

whereas the hi-expectancy experimental subjects had lower expectancies than the hi-expectancy control subjects. Whereas the Tylenol <sup>®</sup>3 group had slightly lower expectations than the hi-expectancy control group and higher expectations than the experimental subjects.

Although all subjects received the equivalent of the pharmacologically active analgesic ingredients found in Tylenol <sup>®</sup>3, significant group differences in post-surgical analgesia were observed. In addition to codeine and acetaminophen, Tylenol <sup>®</sup>3 also contains caffeine—an ingredient added to counteract the sedative effects of codeine. It is noteworthy that these groups differences were obtained regardless of the method chosen to measure analgesia (i.e. proportion of subjects experiencing x% of pain relief; pain intensity difference scores, Peak pain intensity difference scores).

It was expected that expectancy levels would determine the extent of post-surgical analgesia reported by subjects — the higher the expectancy the greater the level of analgesia. This prediction was not supported completely. Figure 15 depicts the Sum of Pain Intensity Difference Scores (SPIDS<sup>15</sup>) against expectancy levels by group. It is evident that although Tylenol <sup>®</sup>3 unaltered expectancy subjects did not have the highest expectancy, they experienced the greatest level of analgesia<sup>16</sup>. It is also clear that when verbal expectancies are not altered by past-experience (i.e. experience of the pill(s) in an experimental pain context), they significantly affect the level of analgesia reported by subjects. Whereas both lo-expectancy controls and lo-expectancy experimental subjects reported lower levels of analgesia than the hi-

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<sup>15</sup> Sum of Pain Intensity Difference Scores obtained by summing four pain intensity difference scores.

<sup>16</sup> If other methods of assessing analgesia are used, such as proportion of subjects with 40% pain relief, then hi-expectancy subjects obtained analgesia comparable to the Tylenol <sup>®</sup>3 subjects.



expectancy controls and hi-expectancy experimental subjects, experimental subjects not only had significantly lower expectancy levels than control subjects, but also reported less analgesia. Thus, past-experience with the analgesic in the experimental setting had the effect of dulling the impact of verbal expectancy instructions. This was true, not only for the subjects who received a placebo, but also those who received an active drug in the experimental session.

Because analgesia was measured by subjective estimation of sensation intensity rather than by direct estimates of analgesia (i.e. how much pain relief was experienced), the results should be less sensitive to the possible bias produced by the demand characteristics inherent in the verbal instructions. In this study, when more direct and subjective measures of analgesia are examined (i.e. subjects' ratings of how much analgesia they experienced on a scale of 1-5), similar but more pronounced results were obtained. Clearly, those who received hi-expectancy instruction reported having experienced more analgesia than lo-expectancy subjects. Subjects who received Tylenol <sup>®</sup>3 with unaltered expectations perceived that they had received a much more potent analgesic than any of the other subjects.

Interestingly, there were no significant effects for unpleasantness on most of the measures of analgesia used in the current study. This is somewhat surprising given that the clinical pain following oral surgery has been associated with significant levels of unpleasantness which in the past have been successfully altered by placebo administration (Levine, Gordon and Fields, 1978). Subjects in this study might have undergone slightly less intrusive surgical procedures than the participants of previous

studies. Intuitively, a less intrusive surgical procedure would result in reduced levels of negative emotional appraisal (i.e. unpleasantness).

Surprisingly, however, the hi-expectancy control subjects, who were told that in addition to an analgesic they would also receive an analgesic enhancer, designed to potentiate the pain relieving effects of the analgesic, experienced lower levels of analgesia than the unaltered Tylenol <sup>®</sup>3 group. While the instructions did in fact produce greater expectations of analgesic efficacy than the unaltered expectation group, the expected corresponding relative analgesic effects were not obtained. It is unlikely that the presence of caffeine—an ingredient with no known analgesic properties—in name brand Tylenol <sup>®</sup>3 could account for the difference among subjects who received the name brand Tylenol <sup>®</sup>3 and those who received the prepared analgesic equivalent of Tylenol <sup>®</sup>3. This result suggests that the relationship between expectation of analgesic efficacy and subsequent levels of analgesia experienced may be mediated by another factor such as the robustness of the expectancy. For example, it could be argued that expectancies for Tylenol <sup>®</sup>3 created by McNeil Pharmaceuticals' effective marketing campaign were more robust than expectancies created by verbal instructions. It is plausible that although the higher magnitude of expectations produced by verbal instructions (hi-expectancy control) may be less robust to direct experiential challenge than are expectations that are based on a long history of past-experience (Tylenol <sup>®</sup>3 group). For example, if an individual has, for years, experienced good analgesic effects from a particular analgesic, this individual's belief in the effectiveness of the analgesic might not be altered significantly with one experience in which the analgesic was not effective. If on the other hand, an individual does not experience analgesic

effects from a new analgesic, the individual will likely lower his/her belief in the effectiveness of that particular analgesic. While it provides a direct measure of the magnitude of expectation for pain relief, the visual analogue scale rating of expectation for pain relief used in the study does not provide an index of the robustness of the expectation.

However, other evidence collected in this study support the assumption that the robustness of the expectation may be even more important in determining analgesic effectiveness than the magnitude of expectation. First, it is clear that the prevailing beliefs about Tylenol <sup>®</sup>3 in our society are quite strong. In fact, in this study, fifty-two percent of the subjects rated Tylenol <sup>®</sup>3 as one of the two most effective analgesics available on the market. Second, past-experience with the analgesic in the experimental session had the net effect of dulling the expectancies created with the verbal instructions. The hi-expectancy experimental subjects reported lower levels of expectation than the hi-expectancy controls while the lo-expectancy experimental subjects reported higher levels of expectation than the lo-expectancy controls.

Thus, it is plausible that in this study the relationship between expectancy levels and subsequent analgesia may be mediated by the robustness of the expectation.

The higher levels of analgesia reported by the unaltered expectancy group could also be attributed to a methodological problem. The Tylenol <sup>®</sup>3 subjects are the only subjects who did not have their surgical fees waived as compensation for participation in the study. Instead, these subjects were asked to participate in the study after the surgery if bone removal was required for the extraction of their tooth or teeth. Because relatively little was being asked of these subjects, waiving their surgical fees

was not warranted. Extrapolating from Totman's (1975) interpretation of his results based on the cognitive dissonance theory, subjects who were not expecting to be compensated for their participation would have greater motivation to show positive responses to the analgesic because it would provide them with justification for subjecting themselves to the many demands placed upon<sup>17</sup> them by participating. In this study, no data were collected to test this hypothesis. This explanation does not apply to the unaltered expectancy group in this study because the demands to which they were subjected did not involve much more than they were going to experience anyway. If they had not volunteered to participate in the study, they would still have undergone surgery, received Tylenol <sup>R</sup>3 and experienced post-surgical pain. All that was asked of them was to rate their sensory stimulation. It is unlikely that meeting these demands would justify increased motivation to show positive analgesic effects.

In sum, even though the hi-expectancy control subjects had significantly greater expectations of analgesic efficacy than the Tylenol <sup>R</sup>3 group, they experienced less analgesia. This results could be attributed to a variety of factors including the robustness of the prevailing expectations of Tylenol <sup>R</sup>3 in the general population and/or a procedural difference which may have altered the motivational level of the Tylenol <sup>R</sup>3 group.

A second unexpected result was the absence of within expectancy group differences in expectancy between experimental subjects who received an analgesic versus those who received a placebo. Intuitively, subjects who had first-hand

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<sup>17</sup> Subjects had to rate their pain every hour for the first 3 doses of the medication as well as answer 6 questions a few days after the post-surgical pain subsided.

experience with the analgesic effect of the drug would be expected to have increased expectancy of its effectiveness. Instead, the results show that expectancy levels conveyed by verbal instructions were more important than past-experience with the drug in predicting subjective levels of analgesia. However, past-experience with the analgesic also seems to be important because in this study, past-experience with the analgesic (or the placebo) served to dull the effects of verbal instructions by raising the expectancy of the lo-expectancy experimental subjects and lowering expectancies of the hi-expectancy experimental subjects. This suggests that the robustness of expectation of analgesic efficacy created by verbal instructions can be altered by contradictory experience (past or future) with the analgesic. In a clinical situation, it is not sufficient to rely simply on either expectations or past-experience. Instead, careful orchestration of both factors could maximize analgesic efficacy. Possibly, a clinician who time after time prescribes ineffective treatments to a patient would lose the power of creating a positive set of expectation thus lowering the effectiveness of all subsequent treatment proposed by this clinician.

Convergent evidence was obtained to support the importance of expectancies. In addition to the impact on length of time before returning to work and subjects' perception of analgesic efficacy, expectancies also influenced the quantity of analgesics taken post-surgically. In fact, hi-expectancy subjects took fewer Tylenol <sup>#</sup>3 or Tylenol 3 equivalents than did the lo-expectancy subjects. Moreover, as a group, a smaller proportion of hi-expectancy subjects took other analgesics. Because the oral surgeon's<sup>18</sup> ratings of the difficulty of the procedure did not differ across groups, it is

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<sup>18</sup> The oral surgeon was unaware of the purpose of the study and group assignment.

unlikely that the discrepancy between groups could be accounted for by overall differences in the difficulty of the surgical procedure.

The current clinical practice of treating acute pain as conservatively as possible by prescribing often inadequate analgesic treatment is driven by a concern that patients may develop a dependence or a tolerance to the medication (Melzack, 1990). The results of the current study indicate that this concern may be misguided. When patients are prescribed what they believe is a strong and effective analgesic (such as Tylenol <sup>®</sup>3), they receive adequate pain relief, take fewer dosages of the strong medication and take fewer dosages of other (often less strong) analgesics. This would reduce both the chance of developing tolerance/dependence to the drug and the chance of developing negative expectations about the analgesic.

**In sum**, this study successfully isolated the effects of expectancy in an experimental context in which a well-controlled experimental pain stimulus was used. In line with the results of previous studies in the alcohol literature, the results of this study lead to the conclusion that in the experimental pain context, expectancies of analgesic efficacy were a more powerful determinant of analgesia and of the experience of drug side-effects than was the presence or absence of pharmacological ingredients found in Tylenol <sup>®</sup>3. Although the drug itself did produce some analgesic effects in the lo-expectancy/analgesic group, these were not robust enough to achieve statistical significance in a sample of 60 subjects.

The study also demonstrated the robustness of the effects of expectancy in the course of recovery from post-surgical pain. Significant effects for expectancy were observed for measures of analgesia which involve direct estimates of sensation

magnitude not believed to be as sensitive to response bias which may be produced by the demand characteristics inherent in the instructions. Similar effects were also obtained for the subjects' ratings of perceived analgesic efficacy, a more subjective estimate of analgesia.

Convergent evidence also pointed to the importance of creating a positive set of expectancies of analgesic efficacy in a clinical pain setting. High expectancies led to quicker return to work and reduced intake of narcotic and non-narcotic analgesics.

### **Future Research**

The results of the study raise important questions about the mechanism by which cognitive factors can influence perception of experimental pain stimuli. One of the mechanisms postulated to explain the effects of expectation on subsequent experience of analgesia involved selective monitoring of the sensations by subjects. Another more compelling mechanism involved the influence of attentional sets on neuropsychophysiological processing of pain. It has been demonstrated in studies with primates that attentional sets can influence the size of receptive fields of wide dynamic range neurons and nociceptive specific neurons and in turn influence pain perception. Two lines of research need to be addressed in order to generalize these findings to humans: 1) experimental evidence to show that as was demonstrated with monkeys, attentional sets in humans can significantly alter pain perception; 2) Demonstration that attentional sets can interact with an analgesic to maximize or to minimize its pharmacological effects. The first line of research would involve testing the effects of attentional sets on pain perception. In one instance, subjects would rate the intensity of painful thermal stimuli in a condition in which they are rewarded for accurate

discrimination of thermal stimuli (focus attention condition). In another instance, subjects would rate the same stimuli in a condition in which they are rewarded to memorize sequences of numbers or letters that are presented visually (distraction condition). Based on the results of the work done with primates, subjects would be expected to rate the stimuli as relatively less intense in the distraction condition as they would in the focus attention condition. Because measuring the size of receptive fields in the dorsal horn is an intrusive procedure, it is unlikely that it could be performed in humans. This is why an accurate replication, in a human sample, of the findings obtained with primates is so appealing. It would allow us to make generalization for a human sample of the neurological mechanism of action found in primates.

Furthering the understanding of the role of attentional sets on analgesic efficacy could be achieved in a study similar to the one presented above. In this case, the subjects would be subjected to the two attentional conditions 45-60 minutes after ingesting a potent analgesic. Such a demonstration would explain the prevailing knowledge that patients who have cognitive styles which incite them to focus attention on sensations tend to report more discomfort than those who use distracting strategies.

Clearly, more work needs to be done to clarify the mechanism by which both the magnitude and the robustness of expectation for analgesic efficacy alter analgesia. Although the present study suggest that both the magnitude and the robustness of expectation are important in predicting subsequent analgesic effects, the determination of the conditions under which these two factors influence analgesic effect is necessary. It is also important to evaluate the conditions under which maximal strength and magnitude of expectations can be created. This line of research is especially relevant



because an understanding of the relation of expectation to treatment effectiveness is crucial if we want to maximize the effectiveness of both pharmacological and non-pharmacological analgesic treatments.

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**APPENDIX A**  
**PAST EXPERIENCE QUESTIONNAIRE**

# PAST EXPERIENCE QUESTIONNAIRE

160

Name: \_\_\_\_\_ Date: \_\_\_\_\_ Age: \_\_\_\_\_

Please take a few minutes to recall and to describe the most painful experience you have ever had.

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Please evaluate how strong the pain was and how unpleasant the feeling was by putting a line across the scales below.

\_\_\_\_\_

not intense  
at all

most intense  
pain imaginable

\_\_\_\_\_

not unpleasant  
at all

most unpleasant  
feeling  
imaginable

If you can recall another very strong painful experience, please describe it and rate its intensity and unpleasantness.

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\_\_\_\_\_

not intense  
at all

most intense  
pain imaginable

\_\_\_\_\_

not unpleasant  
at all

most unpleasant  
feeling  
imaginable



Please describe the painful experiences you have had which lasted more than two consecutive days.

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<u>Experience #</u>	<u>Describe the pain</u>	<u>When</u>	<u>How Long</u>	<u>Medication Taken</u>
---------------------	--------------------------	-------------	-----------------	-------------------------

1.

2.

3.

4.

On average, how many analgesics (ie: aspirin, codeine) do you take per month?

On average, please rate how effective an analgesic is for you

does not get rid of any pain	_____	gets rid of all the pain
---------------------------------	-------	-----------------------------

Please check the analgesic treatments you have used in the past and indicate the approximate number of times

YES	NO	# of times
-----	----	------------

aspirin		
morphine		
codeine (include 217, 222, 292 Sinutab with codeine)		
other opiates		
Tylenol		
Tylenol <sup>®</sup> 3		
Dristan		
Anacin		
hypnosis		
acupuncture		
chiropractics		
relaxation therapy		
Transcutaneous electrical nerve stimulation		

Are you allergic to any of these drugs? YES \_\_\_\_ NO \_\_\_\_

1 6 2

If yes, which one(s)?

Of the pain treatments listed above, which do you think would be best at reducing pain (choose from the treatments you have used and from the treatments you have not used).

\_\_\_\_\_  
\_\_\_\_\_

Of the pain treatments listed above, which do you think would be worse at reducing pain (choose from the treatments you have used and from the treatments you have not used).

\_\_\_\_\_  
\_\_\_\_\_

Do you take medication on a regular basis? YES \_\_\_\_ NO \_\_\_\_

If yes, please indicate the name of the medication, the number of times you take it.

Name \_\_\_\_\_

# of times \_\_\_\_\_

Please briefly describe the medical reason for which you use this medication.

Do you suffer from any of the following medical conditions? Please indicate which one(s) by drawing a circle around its name.

Hepatic diseases

Emphysema

Kyphoscoliosis

Obesity

Asthma

Pregnancy

Allergies (if yes, please indicate the things  
to which you are allergic)

**What stories have you heard from your friends or family members about getting wisdom teeth out?**

**163**

---

---

---

**How do you expect surgery to be today?**

---

**How do you expect recovery to be?**

---

**What is your experience with dentists?**

---

**APPENDIX B**  
**EXPECTANCY QUESTIONNAIRE**

How do you think the capsule(s) will affect your blood pressure during the next hour?

will decrease my blood pressure to a minimum level

will increase my blood pressure to a maximum level

How do you think the capsule(s) will affect your sensitivity to experimental pain during the next hour?

will not affect my sensitivity to pain at all

will make me insensitive to pain

How do you think the capsule(s) will affect your heart rate during the next hour?

will reduce my heart rate to a minimum level

will increase my heart rate to a maximum level

How nervous do you feel right now?

as relaxed as could be

the most nervous possible

How do you think the capsule(s) will affect your nervous feeling?

will not change how nervous I am

will take away all the nervous feeling

How do you think the capsule(s) affected your blood pressure?

decreased my blood pressure to a minimum level

increased my blood pressure to a maximum level

How do you think the capsule(s) affected your sensitivity to pain?

did not affect my sensitivity to pain at all

made me insensitive to pain

How do you think the capsule(s) affected your heart rate?

reduced my heart rate to a minimum level

increased my heart rate to a maximum level

How nervous do you feel right now?

as relaxed as could be

the most nervous possible

How do you think the capsule(s) affected your nervous feeling?

did not change how nervous I felt

took away all the nervous feeling

**APPENDIX C**  
**SPIELBERGER TRAIT AND STATE ANXIETY INVENTORY**

# SELF-EVALUATION QUESTIONNAIRE

168

Developed by Charles D. Spielberger

in collaboration with

R. L. Gorsuch, R. Lushene, P. R. Vagg, and G. A. Jacobs

STAI Form Y-1

Name \_\_\_\_\_ Date \_\_\_\_\_ S \_\_\_\_\_

Age \_\_\_\_\_ Sex: M \_\_\_\_\_ F \_\_\_\_\_ T \_\_\_\_\_

**DIRECTIONS:** A number of statements which people have used to describe themselves are given below. Read each statement and then blacken in the appropriate circle to the right of the statement to indicate how you feel *right now*, that is, *at this moment*. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

VERY MUCH SO  
MODERATELY SO  
SOMEWHAT  
NOT AT ALL

- |                                                            |   |   |   |   |
|------------------------------------------------------------|---|---|---|---|
| 1. I feel calm .....                                       | 1 | 2 | 3 | 4 |
| 2. I feel secure .....                                     | 1 | 2 | 3 | 4 |
| 3. I am tense .....                                        | 1 | 2 | 3 | 4 |
| 4. I feel strained .....                                   | 1 | 2 | 3 | 4 |
| 5. I feel at ease .....                                    | 1 | 2 | 3 | 4 |
| 6. I feel upset .....                                      | 1 | 2 | 3 | 4 |
| 7. I am presently worrying over possible misfortunes ..... | 1 | 2 | 3 | 4 |
| 8. I feel satisfied .....                                  | 1 | 2 | 3 | 4 |
| 9. I feel frightened .....                                 | 1 | 2 | 3 | 4 |
| 10. I feel comfortable .....                               | 1 | 2 | 3 | 4 |
| 11. I feel self-confident .....                            | 1 | 2 | 3 | 4 |
| 12. I feel nervous .....                                   | 1 | 2 | 3 | 4 |
| 13. I am jittery .....                                     | 1 | 2 | 3 | 4 |
| 14. I feel indecisive .....                                | 1 | 2 | 3 | 4 |
| 15. I am relaxed .....                                     | 1 | 2 | 3 | 4 |
| 16. I feel content .....                                   | 1 | 2 | 3 | 4 |
| 17. I am worried .....                                     | 1 | 2 | 3 | 4 |
| 18. I feel confused .....                                  | 1 | 2 | 3 | 4 |
| 19. I feel steady .....                                    | 1 | 2 | 3 | 4 |
| 20. I feel pleasant .....                                  | 1 | 2 | 3 | 4 |



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**APPENDIX D**  
**TELLEGEN ABSORPTION SCALE**

## ABSORPTION QUESTIONNAIRE

Name:

Date:

- |     |                                                                                                                                                                                                        |      |       |
|-----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|-------|
| 1)  | Sometimes I feel and experience things as I did when I was a child                                                                                                                                     | TRUE | FALSE |
| 2)  | I can become deeply involved when reading or hearing about someone else's experience                                                                                                                   | TRUE | FALSE |
| 3)  | When I watch a boat on the lake, I can almost feel what it would be like to be on it                                                                                                                   | TRUE | FALSE |
| 4)  | I can be greatly moved by eloquent or poetic language                                                                                                                                                  | TRUE | FALSE |
| 5)  | While watching a movie, a T.V. show, or a play, I may become so involved that I forget about myself and my surroundings and experience the story as if it were real and as if I were taking part in it | TRUE | FALSE |
| 6)  | If I stare at a picture and then look away from it, I can sometimes "see" an image of the picture, almost as if I were still looking at it                                                             | TRUE | FALSE |
| 7)  | Sometimes I feel as if my mind could envelop the whole world                                                                                                                                           | TRUE | FALSE |
| 8)  | I like to watch cloud shapes change in the sky                                                                                                                                                         | TRUE | FALSE |
| 9)  | If I wish, I can imagine (or daydream) some things so vividly that they hold my attention in the way that a good movie or story does                                                                   | TRUE | FALSE |
| 10) | I sometimes "step outside" my usual self and experience an entirely different state of being                                                                                                           | TRUE | FALSE |
| 11) | I think I really know what some people mean when they talk about mystical experiences                                                                                                                  | TRUE | FALSE |
| 12) | Textures such as wool, sand, and wood, can sometimes remind me of colors or music                                                                                                                      | TRUE | FALSE |

- |                                                                                                                                                                                      |      |       |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|-------|
| 13) Sometimes I experience things as if they were real                                                                                                                               | TRUE | FALSE |
| 14) When I listen to music, I get so caught up in it that I don't notice anything else                                                                                               | TRUE | FALSE |
| 15) If I wish, I can imagine that my body is so heavy that I could not move it if I wanted to                                                                                        | TRUE | FALSE |
| 16) Often I can somehow sense the presence of another person before I can actually see or hear him or her                                                                            | TRUE | FALSE |
| 17) The crackle and flames of a wood fire stimulate my imagination                                                                                                                   | TRUE | FALSE |
| 18) It is sometimes possible for me to be completely immersed in nature or in art and to feel as if my whole state of consciousness has somehow been temporarily altered             | TRUE | FALSE |
| 19) I can sometimes recollect certain past experiences in my life                                                                                                                    | TRUE | FALSE |
| 20) I am able to wander off into my own thoughts while doing a routine task and actually forget that I am doing the task, and then find a few minutes later that I have completed it | TRUE | FALSE |
| 21) I have attempted to write poetry or fiction                                                                                                                                      | TRUE | FALSE |
| 22) Different colors have distinctive and special meaning to me                                                                                                                      | TRUE | FALSE |
| 23) Things that might seem meaningless to others often make sense to me                                                                                                              | TRUE | FALSE |
| 24) While acting in a play, I think I could really feel the emotions of character and "become" him/her for the time being, forgetting both myself and the audience                   | TRUE | FALSE |
| 25) My thoughts often don't occur as words but as visual images                                                                                                                      | TRUE | FALSE |

26)	When listening to organ music or other powerful music, I sometimes feel as if I am being lifted in the air	TRUE	FALSE
27)	I often take delight in small things (like 5-pointed stars shapes or the colors in soap bubbles)	TRUE	FALSE
28)	Sometimes I can change noise into music by the way I listen to it	TRUE	FALSE
29)	Some of my most vivid memories are called up by scents and smells	TRUE	FALSE
30)	Certain pieces of music remind me of pictures or moving patterns of color	TRUE	FALSE
31)	I often know what someone is going to say before he/she says it	TRUE	FALSE
32)	I often have "physical memories", for example, after I have been swimming I may still feel like I am in the water	TRUE	FALSE
33)	The sound of a voice can be so fascinating to me that I can just go on listening to it	TRUE	FALSE
34)	At times I somehow feel the presence of someone who is not physically there	TRUE	FALSE
35)	Sometimes thoughts and images come to me without the slightest effort on my part	TRUE	FALSE
36)	I find that different odors have different colors	TRUE	FALSE
37)	I can be deeply moved by a sunset	TRUE	FALSE

**APPENDIX E**  
**SIDE-EFFECT CHECKLIST**

**SIDE-EFFECTS QUESTIONNAIRE**

Please circle the side-effects you are experiencing now

EXCESSIVE SWEATING

ITCHING

HEADACHE

BACKACHE

NAUSEA

DIZZINESS

BREATHING DIFFICULTIES

STOMACH CRAMPS

DROWSINESS

BLURRED VISION

WATERY EYES

NUMBNESS OF THE SKIN

INCREASED HEART RATE

INCREASED TENSION

SKIN RASH

EUPHORIA

SLEEPY

DRY MOUTH

DIFFICULTY SWALLOWING

ENERGETIC

DEPRESSION

**APPENDIX F**  
**PRE-SURGERY QUESTIONNAIRE**

## PRE SURGERY QUESTIONNAIRE (1)

**Please indicate on the line below how nervous you feel right now:**

as relaxed as  
could be

the most nervous  
possible

**How much pain do you think you will experience during surgery?**

no pain at all most intense pain possible

**How unpleasant will the feeling be during surgery?**

not unpleasant  
at all

most unpleasant  
possible

**How much pain do you think you will experience when the freezing wears off?**

no pain at all most intense  
pain possible

**How unpleasant do you think the feeling in your mouth will be when the freezing wears off?**

not unpleasant  
at all

most unpleasant  
possible

**How effective do you think the pain medication will be at relieving the feeling after the freezing wears off?**

will not reduce pain at all

will get rid of all the pain



**APPENDIX G**  
**POST-SURGERY QUESTIONNAIRE**

**POST SURGERY INTERVIEW**

a) Please describe how smooth you think the surgery was

the procedure  
could not have  
gone worse

the procedure  
could not have  
gone better

b) Please describe how much pain you felt during the surgery

no pain  
at all

most intense  
feeling imaginable

c) How unpleasant was the feeling during surgery?

not unpleasant  
at all

most unpleasant  
imaginable

d) How much pain do you expect to get after the effects of the freezing wear off?

no pain  
at all

most intense  
pain imaginable

What do you think will cause this pain?



**APPENDIX H**  
**POST-SURGERY HOME QUESTIONNAIRE**

## POST-SURGERY PAIN QUESTIONNAIRE

Name: \_\_\_\_\_  
time you took your first pain capsule: \_\_\_\_\_

Immediately after you take your pain capsule(s), please rate the intensity and the unpleasantness of the pain on the lines below + CHECK OFF WORDS

INTENSITY

no sensation at all |-----| pain as strong as could be

UNPLEASANTNESS

not unpleasant at all |-----| as unpleasant as could be

Thirty minutes after you take the pain capsule(s), please rate the intensity and unpleasantness of the pain on the lines below:

INTENSITY

no sensation at all |-----| pain as strong as could be

UNPLEASANTNESS

not unpleasant at all |-----| as unpleasant as could be

One hour after you have taken your pain capsule(s) rate the intensity and the unpleasantness of the pain on the lines below:

INTENSITY

no sensation at all |-----| pain as strong as could be

UNPLEASANTNESS

not unpleasant at all |-----| as unpleasant as could be

- |                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                   |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p><b>1</b></p> <p>1. flickering <input type="checkbox"/></p> <p>2. quivering <input type="checkbox"/></p> <p>3. pulsing <input type="checkbox"/></p> <p>4. throbbing <input type="checkbox"/></p> <p>5. beating <input type="checkbox"/></p> <p>6. pounding <input type="checkbox"/></p> | <p><b>2</b></p> <p>1. jumping <input type="checkbox"/></p> <p>2. flashing <input type="checkbox"/></p> <p>3. shooting <input type="checkbox"/></p>                                                                                       | <p><b>3</b></p> <p>1. pricking <input type="checkbox"/></p> <p>2. boring <input type="checkbox"/></p> <p>3. drilling <input type="checkbox"/></p> <p>4. stabbing <input type="checkbox"/></p> <p>5. lancing <input type="checkbox"/></p> | <p><b>4</b></p> <p>1. sharp <input type="checkbox"/></p> <p>2. cutting <input type="checkbox"/></p> <p>3. lacerating <input type="checkbox"/></p>                                                                                                 |
| <p><b>5</b></p> <p>1. pinching <input type="checkbox"/></p> <p>2. pressing <input type="checkbox"/></p> <p>3. gnawing <input type="checkbox"/></p> <p>4. cramping <input type="checkbox"/></p> <p>5. crushing <input type="checkbox"/></p>                                                | <p><b>6</b></p> <p>1. tugging <input type="checkbox"/></p> <p>2. pulling <input type="checkbox"/></p> <p>3. wrenching <input type="checkbox"/></p>                                                                                       | <p><b>7</b></p> <p>1. hot <input type="checkbox"/></p> <p>2. burning <input type="checkbox"/></p> <p>3. scalding <input type="checkbox"/></p> <p>4. searing <input type="checkbox"/></p>                                                 | <p><b>8</b></p> <p>1. tingling <input type="checkbox"/></p> <p>2. itchy <input type="checkbox"/></p> <p>3. smarting <input type="checkbox"/></p> <p>4. stinging <input type="checkbox"/></p>                                                      |
| <p><b>9</b></p> <p>1. dull <input type="checkbox"/></p> <p>2. sore <input type="checkbox"/></p> <p>3. hurting <input type="checkbox"/></p> <p>4. aching <input type="checkbox"/></p> <p>5. heavy <input type="checkbox"/></p>                                                             | <p><b>10</b></p> <p>1. tender <input type="checkbox"/></p> <p>2. taut <input type="checkbox"/></p> <p>3. rasping <input type="checkbox"/></p> <p>4. splitting <input type="checkbox"/></p>                                               | <p><b>11</b></p> <p>1. tiring <input type="checkbox"/></p> <p>2. exhausting <input type="checkbox"/></p>                                                                                                                                 | <p><b>12</b></p> <p>1. sickening <input type="checkbox"/></p> <p>2. suffocating <input type="checkbox"/></p>                                                                                                                                      |
| <p><b>13</b></p> <p>1. fearful <input type="checkbox"/></p> <p>2. frightful <input type="checkbox"/></p> <p>3. terrifying <input type="checkbox"/></p>                                                                                                                                    | <p><b>14</b></p> <p>1. punishing <input type="checkbox"/></p> <p>2. grueling <input type="checkbox"/></p> <p>3. cruel <input type="checkbox"/></p> <p>4. vicious <input type="checkbox"/></p> <p>5. killing <input type="checkbox"/></p> | <p><b>15</b></p> <p>1. wretched <input type="checkbox"/></p> <p>2. blinding <input type="checkbox"/></p>                                                                                                                                 | <p><b>16</b></p> <p>1. annoying <input type="checkbox"/></p> <p>2. troublesome <input type="checkbox"/></p> <p>3. miserable <input type="checkbox"/></p> <p>4. intense <input type="checkbox"/></p> <p>5. unbearable <input type="checkbox"/></p> |
| <p><b>17</b></p> <p>1. spreading <input type="checkbox"/></p> <p>2. radiating <input type="checkbox"/></p> <p>3. penetrating <input type="checkbox"/></p> <p>4. piercing <input type="checkbox"/></p>                                                                                     | <p><b>18</b></p> <p>1. tight <input type="checkbox"/></p> <p>2. numb <input type="checkbox"/></p> <p>3. drawing <input type="checkbox"/></p> <p>4. squeezing <input type="checkbox"/></p> <p>5. tearing <input type="checkbox"/></p>     | <p><b>19</b></p> <p>1. cool <input type="checkbox"/></p> <p>2. cold <input type="checkbox"/></p> <p>3. freezing <input type="checkbox"/></p>                                                                                             | <p><b>20</b></p> <p>1. nagging <input type="checkbox"/></p> <p>2. nauseating <input type="checkbox"/></p> <p>3. agonizing <input type="checkbox"/></p> <p>4. dreadful <input type="checkbox"/></p> <p>5. torturing <input type="checkbox"/></p>   |

183

no sensation  
at all

pain as strong  
as could be

not unpleasant  
at all

as unpleasant  
as could be

**INTENSITY**

no sensation at all

pain as strong as could be

not unpleasant  
at all

as unpleasant  
as could be

time you took your second pain capsule: \_\_\_\_\_

184

Immediately after you take your pain capsule(s), please rate the intensity and the unpleasantness of the pain on the lines below **AND CHECK OFF WORDS**

INTENSITY

no sensation at all |-----| pain as strong as could be

UNPLEASANTNESS

not unpleasant at all |-----| as unpleasant as could be

Thirty minutes after you take the pain capsule(s), please rate the intensity and unpleasantness of the pain on the lines below:

INTENSITY

no sensation at all |-----| pain as strong as could be

UNPLEASANTNESS

not unpleasant at all |-----| as unpleasant as could be

One hour after you have taken your pain capsule(s) rate the intensity and the unpleasantness of the pain on the lines below:

INTENSITY

no sensation at all |-----| pain as strong as could be

UNPLEASANTNESS

not unpleasant at all |-----| as unpleasant as could be

two hours after you have taken your pain capsule(s) rate the intensity and the unpleasantness of the pain on the lines below:

INTENSITY

no sensation at all |-----| pain as strong as could be



- |                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                   |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p><b>1</b></p> <p>1. flickering <input type="checkbox"/></p> <p>2. quivering <input type="checkbox"/></p> <p>3. pulsing <input type="checkbox"/></p> <p>4. throbbing <input type="checkbox"/></p> <p>5. beating <input type="checkbox"/></p> <p>6. pounding <input type="checkbox"/></p> | <p><b>2</b></p> <p>1. jumping <input type="checkbox"/></p> <p>2. flashing <input type="checkbox"/></p> <p>3. shooting <input type="checkbox"/></p>                                                                                       | <p><b>3</b></p> <p>1. pricking <input type="checkbox"/></p> <p>2. boring <input type="checkbox"/></p> <p>3. drilling <input type="checkbox"/></p> <p>4. stabbing <input type="checkbox"/></p> <p>5. lancing <input type="checkbox"/></p> | <p><b>4</b></p> <p>1. sharp <input type="checkbox"/></p> <p>2. cutting <input type="checkbox"/></p> <p>3. lacerating <input type="checkbox"/></p>                                                                                                 |
| <p><b>5</b></p> <p>1. pinching <input type="checkbox"/></p> <p>2. pressing <input type="checkbox"/></p> <p>3. gnawing <input type="checkbox"/></p> <p>4. cramping <input type="checkbox"/></p> <p>5. crushing <input type="checkbox"/></p>                                                | <p><b>6</b></p> <p>1. tugging <input type="checkbox"/></p> <p>2. pulling <input type="checkbox"/></p> <p>3. wrenching <input type="checkbox"/></p>                                                                                       | <p><b>7</b></p> <p>1. hot <input type="checkbox"/></p> <p>2. burning <input type="checkbox"/></p> <p>3. scalding <input type="checkbox"/></p> <p>4. searing <input type="checkbox"/></p>                                                 | <p><b>8</b></p> <p>1. tingling <input type="checkbox"/></p> <p>2. itchy <input type="checkbox"/></p> <p>3. smarting <input type="checkbox"/></p> <p>4. stinging <input type="checkbox"/></p>                                                      |
| <p><b>9</b></p> <p>1. dull <input type="checkbox"/></p> <p>2. sore <input type="checkbox"/></p> <p>3. hurting <input type="checkbox"/></p> <p>4. aching <input type="checkbox"/></p> <p>5. heavy <input type="checkbox"/></p>                                                             | <p><b>10</b></p> <p>1. tender <input type="checkbox"/></p> <p>2. taut <input type="checkbox"/></p> <p>3. rasping <input type="checkbox"/></p> <p>4. splitting <input type="checkbox"/></p>                                               | <p><b>11</b></p> <p>1. tiring <input type="checkbox"/></p> <p>2. exhausting <input type="checkbox"/></p>                                                                                                                                 | <p><b>12</b></p> <p>1. sickening <input type="checkbox"/></p> <p>2. suffocating <input type="checkbox"/></p>                                                                                                                                      |
| <p><b>13</b></p> <p>1. fearful <input type="checkbox"/></p> <p>2. frightful <input type="checkbox"/></p> <p>3. terrifying <input type="checkbox"/></p>                                                                                                                                    | <p><b>14</b></p> <p>1. punishing <input type="checkbox"/></p> <p>2. grueling <input type="checkbox"/></p> <p>3. cruel <input type="checkbox"/></p> <p>4. vicious <input type="checkbox"/></p> <p>5. killing <input type="checkbox"/></p> | <p><b>15</b></p> <p>1. wretched <input type="checkbox"/></p> <p>2. blinding <input type="checkbox"/></p>                                                                                                                                 | <p><b>16</b></p> <p>1. annoying <input type="checkbox"/></p> <p>2. troublesome <input type="checkbox"/></p> <p>3. miserable <input type="checkbox"/></p> <p>4. intense <input type="checkbox"/></p> <p>5. unbearable <input type="checkbox"/></p> |
| <p><b>17</b></p> <p>1. spreading <input type="checkbox"/></p> <p>2. radiating <input type="checkbox"/></p> <p>3. penetrating <input type="checkbox"/></p> <p>4. piercing <input type="checkbox"/></p>                                                                                     | <p><b>18</b></p> <p>1. tight <input type="checkbox"/></p> <p>2. numb <input type="checkbox"/></p> <p>3. drawing <input type="checkbox"/></p> <p>4. squeezing <input type="checkbox"/></p> <p>5. tearing <input type="checkbox"/></p>     | <p><b>19</b></p> <p>1. cool <input type="checkbox"/></p> <p>2. cold <input type="checkbox"/></p> <p>3. freezing <input type="checkbox"/></p>                                                                                             | <p><b>20</b></p> <p>1. nagging <input type="checkbox"/></p> <p>2. nauseating <input type="checkbox"/></p> <p>3. agonizing <input type="checkbox"/></p> <p>4. dreadful <input type="checkbox"/></p> <p>5. torturing <input type="checkbox"/></p>   |

UNPLEASANTNESS

186

not unpleasant  
at all

as unpleasant  
as could be

three hours after you have taken your pain capsule(s) rate the intensity and the unpleasantness of the pain on the lines below:

**INTENSITY**

no sensation at all

pain as strong as could be

**UNPLEASANTNESS**

not unpleasant as unpleasant  
at all as could be

time you took your third pain capsule: \_\_\_\_\_

Immediately after you take your pain capsule(s), please rate the intensity and the unpleasantness of the pain on the lines below AND CHECK OFF WORDS

INTENSITY

no sensation at all pain as strong as could be

UNPLEASANTNESS

not unpleasant at all as unpleasant as could be

Thirty minutes after you take the pain capsule(s), please rate the intensity and unpleasantness of the pain on the lines below:

INTENSITY

no sensation at all pain as strong as could be

UNPLEASANTNESS

not unpleasant at all as unpleasant as could be

One hour after you have taken your pain capsule(s) rate the intensity and the unpleasantness of the pain on the lines below:

INTENSITY

no sensation at all pain as strong as could be

UNPLEASANTNESS

not unpleasant at all as unpleasant as could be

two hours after you have taken your pain capsule(s) rate the intensity and the unpleasantness of the pain on the lines below:

INTENSITY

no sensation at all pain as strong as could be

- |                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                   |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p><b>1</b></p> <p>1. flickering <input type="checkbox"/></p> <p>2. quivering <input type="checkbox"/></p> <p>3. pulsing <input type="checkbox"/></p> <p>4. throbbing <input type="checkbox"/></p> <p>5. beating <input type="checkbox"/></p> <p>6. pounding <input type="checkbox"/></p> | <p><b>2</b></p> <p>1. jumping <input type="checkbox"/></p> <p>2. flashing <input type="checkbox"/></p> <p>3. shooting <input type="checkbox"/></p>                                                                                       | <p><b>3</b></p> <p>1. pricking <input type="checkbox"/></p> <p>2. boring <input type="checkbox"/></p> <p>3. drilling <input type="checkbox"/></p> <p>4. stabbing <input type="checkbox"/></p> <p>5. lancing <input type="checkbox"/></p> | <p><b>4</b></p> <p>1. sharp <input type="checkbox"/></p> <p>2. cutting <input type="checkbox"/></p> <p>3. lacerating <input type="checkbox"/></p>                                                                                                 |
| <p><b>5</b></p> <p>1. pinching <input type="checkbox"/></p> <p>2. pressing <input type="checkbox"/></p> <p>3. gnawing <input type="checkbox"/></p> <p>4. cramping <input type="checkbox"/></p> <p>5. crushing <input type="checkbox"/></p>                                                | <p><b>6</b></p> <p>1. tugging <input type="checkbox"/></p> <p>2. pulling <input type="checkbox"/></p> <p>3. wrenching <input type="checkbox"/></p>                                                                                       | <p><b>7</b></p> <p>1. hot <input type="checkbox"/></p> <p>2. burning <input type="checkbox"/></p> <p>3. scalding <input type="checkbox"/></p> <p>4. searing <input type="checkbox"/></p>                                                 | <p><b>8</b></p> <p>1. tingling <input type="checkbox"/></p> <p>2. itchy <input type="checkbox"/></p> <p>3. smarting <input type="checkbox"/></p> <p>4. stinging <input type="checkbox"/></p>                                                      |
| <p><b>9</b></p> <p>1. dull <input type="checkbox"/></p> <p>2. sore <input type="checkbox"/></p> <p>3. hurting <input type="checkbox"/></p> <p>4. aching <input type="checkbox"/></p> <p>5. heavy <input type="checkbox"/></p>                                                             | <p><b>10</b></p> <p>1. tender <input type="checkbox"/></p> <p>2. taut <input type="checkbox"/></p> <p>3. rasping <input type="checkbox"/></p> <p>4. splitting <input type="checkbox"/></p>                                               | <p><b>11</b></p> <p>1. tiring <input type="checkbox"/></p> <p>2. exhausting <input type="checkbox"/></p>                                                                                                                                 | <p><b>12</b></p> <p>1. sickening <input type="checkbox"/></p> <p>2. suffocating <input type="checkbox"/></p>                                                                                                                                      |
| <p><b>13</b></p> <p>1. fearful <input type="checkbox"/></p> <p>2. frightful <input type="checkbox"/></p> <p>3. terrifying <input type="checkbox"/></p>                                                                                                                                    | <p><b>14</b></p> <p>1. punishing <input type="checkbox"/></p> <p>2. grueling <input type="checkbox"/></p> <p>3. cruel <input type="checkbox"/></p> <p>4. vicious <input type="checkbox"/></p> <p>5. killing <input type="checkbox"/></p> | <p><b>15</b></p> <p>1. wretched <input type="checkbox"/></p> <p>2. blinding <input type="checkbox"/></p>                                                                                                                                 | <p><b>16</b></p> <p>1. annoying <input type="checkbox"/></p> <p>2. troublesome <input type="checkbox"/></p> <p>3. miserable <input type="checkbox"/></p> <p>4. intense <input type="checkbox"/></p> <p>5. unbearable <input type="checkbox"/></p> |
| <p><b>17</b></p> <p>1. spreading <input type="checkbox"/></p> <p>2. radiating <input type="checkbox"/></p> <p>3. penetrating <input type="checkbox"/></p> <p>4. piercing <input type="checkbox"/></p>                                                                                     | <p><b>18</b></p> <p>1. tight <input type="checkbox"/></p> <p>2. numb <input type="checkbox"/></p> <p>3. drawing <input type="checkbox"/></p> <p>4. squeezing <input type="checkbox"/></p> <p>5. tearing <input type="checkbox"/></p>     | <p><b>19</b></p> <p>1. cool <input type="checkbox"/></p> <p>2. cold <input type="checkbox"/></p> <p>3. freezing <input type="checkbox"/></p>                                                                                             | <p><b>20</b></p> <p>1. nagging <input type="checkbox"/></p> <p>2. nauseating <input type="checkbox"/></p> <p>3. agonizing <input type="checkbox"/></p> <p>4. dreadful <input type="checkbox"/></p> <p>5. torturing <input type="checkbox"/></p>   |

UNPLEASANTNESS

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|  
not unpleasant  
at all

|  
as unpleasant  
as could be

three hours after you have taken your pain capsule(s) rate the intensity and the unpleasantness of the pain on the lines below:

INTENSITY

|  
no sensation  
at all

|  
pain as strong  
as could be

UNPLEASANTNESS

|  
not unpleasant  
at all

|  
as unpleasant  
as could be

Please indicate how soon after surgery you were able to eat for the first time (in hours):

Please indicate how soon after surgery you were able to resume your normal eating habits (in hours):

Please indicate how soon after surgery you were able to resume your normal work schedule (in hours or days):

Please indicate how many times you had to take pain medication for the pain due to surgery:

Please indicate how much post surgical pain you experienced compared to what you expected:

|  
I experienced much  
less pain than I  
thought I would have

|  
I experienced much  
more pain than I  
thought I would have

In general, how effective was the pain medication?

- 1) got rid of no pain
- 2) got rid of a bit of pain
- 3) got rid of quite a bit of pain
- 4) got rid of half the pain
- 5) got rid of almost all the pain
- 6) got rid of all the pain

**APPENDIX I**  
**SURGEON QUESTIONNAIRE**

DENTIST QUESTIONNAIRE

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name of patient: \_\_\_\_\_  
name of dentist: \_\_\_\_\_

please describe briefly the extraction you just performed  
(describe extent of tissue damage and bone removal):

Please rate on the line below how difficult you think the surgery was:

\_\_\_\_\_

as easy as could be given the placement of the tooth	as difficult as could be given the placement of the tooth
------------------------------------------------------------	-----------------------------------------------------------------

Given the difficulty of the procedure, how much post-surgical pain  
do you think the patient will experience?

\_\_\_\_\_

no pain at all	excruciating pain
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OTHER COMMENTS:

**APPENDIX J**

**LETTER OF EXPLANATION AND CONSENT FORM FOR SUBJECTS WHO  
PARTICIPATED IN THE EXPERIMENTAL SESSION**



## LETTER OF EXPLANATION

Pain medication is regularly used to control all kinds of pain at home, in clinics and hospitals. While researchers in the area of pain control know some of the mechanisms responsible for pain and pain reduction, little is known about the effects of the way we think or the way we feel pain. This study looks at the effects of some of the ways we think or the way pain medication works for both experimental and clinical pain.

The pain medications used in this study present no risk of side-effects or complication beyond those associated with the pain medication that you will take after surgery. You will be given the medication by mouth. Sometimes, there can be allergies to this medication, but this happens in very rare instances.

In this study, we will ask you to come to the clinic for one visit of 1 1/2 hour before surgery. This visit can be scheduled weekdays between 9 and 5 at your convenience. During the visit, you will be asked to fill out questionnaires about: 1) you past experience with pain and pain medication; 2) how much anxiety you feel; and 3) how you are able to use your imagination. You will also be asked to tell how much pain you feel and how unpleasant the pain is when you receive a series of heat pulses on the inside of your forearms. Then, you will take a pain medication and will again tell how much pain you felt and how unpleasant the pain is when you receive the heat pulses on the inside of your forearms. Since the effect of the pill can last up to 2 1/2 hours, you will be asked not to drive a motor vehicle, a bicycle or to operate heavy machinery for a 1 1/2 hour period after leaving the clinic.

The heat pulses are produced by a hand held device which delivers 5 second heat pulses. At first, you will receive heat pulses which will produce a vague pricking sensation (not everyone reports that these levels are painful). You will be asked to indicate the highest pulse you can tolerate. Then, several pulses of varying temperature will be applied to the inside of your forearm in random order. You will be asked to rate how much the heat pulses hurt and how unpleasant they are. When heat pulses are applied to a participant's forearm, only nerves are stimulated and studies show that there is absolutely no damage to either the skin or the nerves. The instrument which produces the heat pulses is equipped with a device which returns the skin back to its original temperature within five seconds. Many studies have been done with this device and it has been shown to be a safe and reliable instrument for producing short-acting pain for this type of research.

On the day of surgery, you will be asked to answer questions about pain and anxiety and to rate how much pain you feel and how unpleasant the pain is after surgery. You will receive the same treatment from the dentist and the same surgical procedure as patients who do not participate in the study.

All personal information will be held in strict confidence. When published, reports of information collected in this study will not be associated with names of individual participants.

You may terminate your participation at any time without prejudice or jeopardy to your future care. If you decide to participate in this study, the usual clinical surgical fees will be waived to compensate you for your time. If you wish to end your participation during or at the end of the first session, you will have 1/3 of the fees waived. If you wish to end your participation during or after the second session, you will have 2/3 of the fees waived.

If you are interested to participate in the study or if you require more information, please contact Manon Houle at 473-9414.

**CONSENT FORM**

**Title: Psychological and situational variables--  
Their influence on analgesic efficacy**

You are invited to participate in a study done by the Faculty of Dentistry of the University of Western Ontario and the Psychology Department of the University of Western Ontario to look at the effects of the way we think on the effectiveness of pain medication. It is important that you read the letter of explanation and that you understand the general principles which apply to all persons who participate in this study.

1. Your participation is entirely voluntary and you may withdraw at any time without prejudice or jeopardy to your future care,
2. Although the results of the study may not benefit you directly, it may help professional who work with people who suffer from pain to understand how the way we think affects how we feel pain,
3. All personal information obtained from you will be held in strict confidence. When published, reports of information collected in this study will not be associated with the names of individual participants,
4. The usual clinical surgical fees will be waived to compensate you for your time. For those who wish to terminate during or at the end of the first session, one third of the surgical fees will be waived. For those who wish to terminate during or at the end of the second session, two thirds of the surgical fees will be waived,
5. The treatment you will receive from the dentist during surgery, the surgical procedure he/she will use and the treatment you will receive after surgery will be the same as the treatment you would receive if you did not participate in the study.
6. You may withdraw from the study at any time and you will still receive a summary of the results at the end of the study.

I understand that as a participant in this study, I will rate the pain and the unpleasantness of heat pulses on my forearm. I will also receive pain medication under the supervision of Dr. S. Kogon and the dentist assigned to my case. This pain medication presents no risk of side effects or complications beyond those associated with the pain medication I would take after surgery. The pain medication used in the study produce variable levels of pain reduction and minimal side effects in rare cases. I also understand that the pain clinic has all the equipment and personel required to deal with any side-effects I may feel. Further, I understand that I should not drive a car, a bicycle or operate heavy machinery for a two and one half hour period after taking the medication. I have been given a chance to discuss this study and to ask questions about it. I consent to participate in this study.

Signature \_\_\_\_\_ Date \_\_\_\_\_

**APPENDIX K**

**LETTER OF EXPLANATION AND CONSENT FORM  
FOR CONTROL SUBJECTS**

## LETTER OF EXPLANATION

Pain medication is regularly used to control all kinds of pain at home, in clinics and hospitals. While researchers in the area of pain control know some of the mechanisms responsible for pain and pain reduction, little is known about the effects of the way we think about the way we feel pain. This study looks at the effects of our thoughts on the way pain medication works for both experimental and clinical pain.

The pain medications used in this study is the same as the pain medication you would normally take after surgery. As the dentist will tell you, there are sometimes allergies to this medication, but this happens in very rare instances.

In this study, we will ask you to come to the clinic one hour before surgery to complete some questionnaires which will ask you about: 1) your past experience with pain and pain medication; 2) how much anxiety you feel; and 3) how you are able to use your imagination. After surgery, you will be asked to answer questions about pain and anxiety and to rate how much pain and how unpleasant the pain is after surgery. You will receive the same treatment from the dentist and the same surgical procedure as patients who do not participate in the study.

All personal information will be held in strict confidence. When published, reports of information collected in this study will not be associated with names of individual participants.

You may terminate your participation at any time without prejudice or jeopardy to your future care. If you decide to participate in this study, the usual clinical surgical fees will be waived to compensate you for your time.

If you are interested to participate in the study or if you require more information, please contact Manon Houle at 473-9414 (evenings) or 661-3450 (days).

CONSENT FORM

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Title: Psychological and situational variables--  
Their influence on analgesic efficacy

You are invited to participate in a study done by the Faculty of Dentistry of the University of Western Ontario and the Psychology Department of the University of Western Ontario to look at the effects of the way we think on the effectiveness of pain medication. It is important that you read the letter of explanation and that you understand the general principles which apply to all persons who participate in this study.

1. Your participation is entirely voluntary and you may withdraw at any time without prejudice or jeopardy to your future care,
2. Although the results of the study may not benefit you directly, it may help those who work with people who suffer from pain to understand how the way we think affects how we feel pain,
3. All personal information obtained from you will be held in strict confidence. When published, reports of information collected in this study will not be associated with the names of individual participants,
4. The usual clinical surgical fees will be waived to compensate you for your time.
5. The treatment you will receive from the dentist during surgery, the surgical procedure he/she will use and the treatment you will receive after surgery will be the same as the treatment you would receive if you did not participate in the study.
6. You may withdraw from the study at any time and you will still receive a summary of the results at the end of the study.

I understand that as a participant in this study, I will rate how much it hurts and how unpleasant the pain is after surgery. I will also receive pain medication under the supervision of Dr. S. Kogon and the dentist assigned to my case. The pain medication used in the study is the same as the pain medication I would take if I did not participate in the study. The medication produces variable levels of pain reduction and in rare cases minimal side effects. I also understand that the pain clinic has all the equipment and personnel required to deal with any side-effects I may feel. Further, I understand that I should not drive a car, a bicycle or operate heavy machinery for a two and one half hour period after taking the medication. I have been given a chance to discuss this study and to ask questions about it. I consent to participate in this study.

Signature \_\_\_\_\_ Date \_\_\_\_\_